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ARIPIPRAZOLE, OLANZAPINE AND HALOPERIDOL IN THE LONG TERM TREATMENT OF SCHIZOPHRENIA:

The rationale & development of the GiSAS pragmatic randomized controlled trial, a consideration and empirical study of factors associated with recruitment (the GiSAS survey) and the concept of endpoints using a secondary analysis of existing data and a preliminary analysis of GiSAS trial data.

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ABSTRACT

This thesis described the development of a pragmatic, randomized clinical trial evaluating the safety and efficacy of antipsychotic treatment in schizophrenia. In the perspective of highlighting some critical issues of the trial design, the thesis focused on the trial's planning and conduct and on the preliminary analysis of the first followed-up subjects.

Having experienced significant problems in patient recruitment a survey on perceived inclusion barriers and antipsychotic preference was performed. Investigators mainly complained about system-related barriers, and believed in the superiority of second-generation antipsychotics. Taking the cue from these results, strategies were adopted in order to reach the planned target of 800 subjects. Remedial actions included study promotion activities, education initiatives and bursaries, and resulted in a significant improvement of the recruitment rate. Nevertheless, we had to reduce the sample to one third of the original size.

The second part of the thesis focused on the concept of endpoints using a secondary analysis of existing data and a preliminary analysis of GiSAS trial data. The assumption that differences in discontinuation rates reflect differences in effectiveness was reinforced by the results of a pharmaco-epidemiological study comparing the use of reboxetine and SSRIs in a large population sample. The established lack of efficacy of this antidepressant was mirrored by a higher proportion of treatment discontinuations. We explored the baseline characteristics of 114 included subjects and compared the baseline and follow-up variables between those who discontinued study drugs at follow-up and those who did not. Discontinuers' worse outcome was mainly attributable to self reported side-effects.

This thesis highlighted some critical issues on the execution of a pragmatic trial in schizophrenia. The feasibility of the trial design and the concept of endpoints were critically analyzed. The trial mechanism is now fully functional and most problems of its implementation have been identified and contained.

LIST OF ABBREVIATIONS

AD:	Antidepressant
AHA:	American Heart Association
ATP:	Adult Treatment Panel III
BF:	Baseline Form
BMI:	Body-mass index
BPRS:	Brief Psychiatric rating Scale
CATIE:	Clinical Antipsychotic Trials of Intervention Effectiveness
CI:	Confidence Interval
CMHS:	Community mental health services
CONSORT:	Consolidated Standards of Reporting Trials
CUtLASS:	Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia
DSM-IV-TR:	Diagnostic and Statistical Manual of Mental Disorders
ECG:	Electrocardiogram
ECM	[Educazione Continua in Medicina] Continuous education in medicine
EGRIS:	European Group for Research in Schizophrenia
EPS:	Extrapyramidal symptoms
EUFEST:	European First Episode Schizophrenia Trial
FDA:	Food and Drug Administration
FF:	Follow-up form
FGAs:	First-generation antipsychotics
GAF:	Global Assessment of Functioning
GiSAS:	Italian Group for the Study of Second-generation Antipsychotics
GP:	General practitioner
GVRS:	Global Vascular Risk Score
HDL:	High Density Lipoprotein

IQWiG:	German Institute for Quality and Efficiency in Health Care
ITT:	Intention to treat
LUNSERS:	Liverpool University Neuroleptic Side Effect Rating Scale
NCEP:	National Cholesterol Education Program
NIMH:	National Institute of Mental Health
NOMAS:	Northern Manhattan Cohort Study
OR:	odds ratio
PANSS:	Positive and Negative Symptom Scale
QLS:	Quality of life
QTc:	Corrected QT interval
RCT:	Randomized controlled trial
SD:	Standard Deviation
SGAs:	Second-generation antipsychotics
SMR :	Standardized mortality ratio
SSN:	[Servizio Sanitario Nazionale] National Health Service
TF:	Treatment Form
Tg:	Triglycerides
SNRI:	Selective Noradrenalin Re-uptake Inhibitor
SSRI:	Selective Serotonin Re-uptake Inhibitor
TF:	Treatment Form
Tg:	Triglycerides
WC:	waist circumference
WHR:	waist-to-hip ratio
WHtR:	waist-to-height ratio

CHAPTER I

GiSAS TRIAL: BACKGROUND, RATIONALE AND METHODS

1. Background

Debate over old versus new antipsychotics

Schizophrenia is a serious and disabling mental illness characterized by positive symptoms (such as delusions and hallucinations) and negative symptoms (such as lack of motivation and social withdrawal). It usually needs long-term therapy and can produce far-reaching effects on personality, cognition, global functioning and quality of life. Antipsychotic drugs are the cornerstone of the pharmacological treatment of schizophrenia. First Generation Antipsychotics (FGAs) are high-affinity antagonists of dopamine D2 receptors. Their short-term benefits in controlling positive psychotic symptoms, together with high rates of neurological side effects, such as parkinsonism, akathisia and tardive dyskinesia, are well documented. However, long-term data are too few and there is no convincing evidence that FGAs exert any effect on the negative symptoms of schizophrenia [1-3].

The introduction of second generation antipsychotics (SGAs) promised enhanced efficacy and safety. While FGAs were characterized by predominant dopaminergic blockade, SGAs had significant affinity for a broader and somewhat diversified range of receptors, especially the serotonin 5-HT2 receptor [4]. Clozapine, the first representative of this new class of drugs, was developed in the early 1960s as an antipsychotic with low affinity with D2 receptors and minimally associated extrapyramidal symptoms (EPS) [5]. Initial enthusiasm for the novelty of the mechanism of action of clozapine, which based on a more potent effect on the symptoms of schizophrenia, was seriously tempered by the occurrence of serious blood dyscrasias and patient deaths. Thus, clozapine was briefly marketed and quickly withdrawn before it recovered its reputation [5, 6] a decade later.

Nonetheless, the introduction of clozapine refuted the hypothesis that EPS and antipsychotic efficacy were linked and paved the way to the search for a new generation of antipsychotics that might be better tolerated and more effective than FGAs. The supposed superiority of SGAs over FGAs was questioned by early reviews [7, 8]. Studies indicated that SGAs are effective in reducing psychotic symptoms and produce few neurological effects. The evidence of their greater efficacy, however, resulted neither consistent nor robust [7, 8]. Moreover, although there is evidence of a lower risk of extrapyramidal side effects, they were reported to cause metabolic side effects like weight gain, dyslipidemia and impaired fasting glucose [9]. Only clozapine, after a bumpy road of withdrawal and review, was clearly more effective in patients whose symptoms do not respond to other antipsychotics, but severe side effects and the need for blood cell count monitoring limit its use in community settings [6, 10, 11].

In a recent meta-analysis, including 150 double-blind trials, some SGAs showed to be more efficacious than FGAs in terms of symptom relief, with small effect sizes for amisulpride, olanzapine and risperidone and with a medium effect size for clozapine [12]. However, most of the trials included in the analysis recruited highly selected samples adopting short-term follow-up and investigator-scored efficacy measures. These features limit the reliability, the external validity, and the generalizability of the results. Moreover, in another meta-analysis focusing on the metabolic side-effects of SGAs, olanzapine and clozapine had the worst profile [13].

Initial enthusiasm for the "atypical" effect of SGAs has gradually waned, while there has been a growing concern about the rapidly escalating costs of this class of medication [14, 15]. Public institutions and researchers have become increasingly suspicious about the evidence on antipsychotic medications, most of

which comes from industry-sponsored trials [16, 17]. Thus, there is need to further investigate the effectiveness of both FGAs and SGAs in pragmatic independent trials [18, 19].

Recent pragmatic findings on antipsychotics

Many worthwhile treatment effects on major outcomes in medicine are only of moderate size and their evaluation requires large-scale studies. RCTs need to be large to minimize systematic bias and random error and to measure treatment effects reliably and precisely. Moreover, they need to be simple to minimize the additional clinical workload and help to maximize widespread collaboration [18-20]. Recently, three landmark independent studies, CATIE, CUtLASS and EUFEST, casted further doubts on the effectiveness of SGAs vs. FGAs in schizophrenia. All those randomized clinical trials (RCTs) shared many features of so-called large and simple trials: sufficient power, few exclusion criteria, sound endpoints and simple study designs (See Table 1).

The US Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study was conducted between 2001 and 2004 at 57 clinical sites in the United States [21]. The trial included both a phase 1 and a phase 2. The phase 1 was a double-blind trial in which patients affected by chronic schizophrenia were randomized under double-blind conditions to one of the SGAs olanzapine, quetiapine, risperidone, ziprasidone or to the FGA perphenazine and followed-up for 18 months. The primary endpoint was time to treatment discontinuation for any cause, chosen to reflect clinical practice. Among the secondary outcomes there were the specific reasons for discontinuation of treatment (e.g. inefficacy or intolerability owing to side effects such as weight gain, extrapyramidal signs, or sedation as judged by the study doctor) [21].

In a subsequent trial (phase 2) those participants who discontinued the first phase because of lack of efficacy were re-randomized to an open-label comparison between clozapine and the other SGAs [22].

In CATIE phase 1 a total of 1,493 patients were enrolled and randomly assigned to treatment and 1,432 (96%) were included in the analysis: olanzapine (n=330), quetiapine (n=329), risperidone (n=333), ziprasidone (n=183) or to the FGA perphenazine (n=257). Overall 74% of patients in the intention-to-treat analysis discontinued the assigned treatment before 18 months. The time to discontinuation of treatment for any reason was longer in the olanzapine group than in the quetiapine group and the risperidone group. By contrast, the difference between the olanzapine group and the perphenazine or the ziprasidone group was not significant. However, the time to discontinuation of treatment for lack of efficacy was longer in the olanzapine group than in the perphenazine group. Referring to antipsychotic safety profile, time until discontinuation owing to intolerable side effects was similar among the groups even with a trend toward statistical significance (P=0.054). However, rates were significantly different: olanzapine was associated with more discontinuation for weight gain or metabolic effects, and perphenezine was associated with more discontinuation for extrapyramidal effects [21].

The UK Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia (CUtLASS) study comprised a pair of smaller open-label trials comparing FGAs vs. SGAs in terms of quality of life (QLS) at one year [23, 24]. The authors considered as clinically meaningful a difference in the QLS scores between the 2 arms of 5 points from baseline to 12 months. In CUtLASS-2, clozapine was compared with the other SGAs in 136 patients non-responders to antipsychotic drugs. In CUtLASS-1, 227 people with schizophrenia were randomized to either the class of FGAs (n=118) or the class of SGAs (n=109), with the exclusion of clozapine.

Contrary to the primary hypothesis, the estimate of 5 points in favor of SGAs was excluded and the apparent advantage for FGAs, an effect opposite to the hypothesis, did not reach statistical significance (P =0.24).

Both the CATIE and the CUtLASS study failed in finding clinically relevant differences between SGAs and FGAs in terms of effectiveness or tolerability [21, 23]. On the other hand, they found clozapine to be more effective in refractory schizophrenia, and the prescription of FGAs to be associated with lower costs and higher quality-adjusted life-years [22, 24-26].

Table 1

Examples of independently funded pragmatic RCT on long-term effectiveness of antipsychotic therapy in schizophrenia.

	CATIE - phase 1	CUtLASS 1	EUFEST	GISAS
DESIGN	Double-blind	Open-label (rater-blinded)	Open-label	Open-label (analyst-blinded)
FOLLOW-UP	18 months	12 months	12 months	12 months
STUDY DRUGS	Olanzapine vs. Perfenazine vs. Quetiapine vs. Risperidone	FGA vs. SGA	Haloperidol vs. [amisulpride, olanzapine, quetiapine, ziprasidone]	Aripiprazole vs. [Olanzapine Haloperidol]
PRIMARY ENDPOINT	Time to study drug discontinuation	Quality of life	Time to study drug discontinuation	Staying on study drug without developing metabolic syndrome
PARTICIPATING CENTERS	57 US	14 UK	50 (14 UE countries)	35 ITA
PATIENTS (NO.)	1,432	227	498	300
FUNDING	NIMH	NHS	EGRIS (Pfizer, AstraZeneca, Sanofi-Aventis)	MNegri (Bristol-Myers Squibb)

The European First Episode Schizophrenia Trial (EUFEST) study was a pragmatic open randomized-controlled trial in which a wide group of European psychiatrists and researchers compared the effectiveness of low doses of haloperidol with SGAs in first-episode schizophrenia [27]. The study hypothesis was based on the conclusions of a meta-regression analysis by Geddes et al. (2000), suggesting that trials demonstrating the inferiority of first- versus second-generation antipsychotics used too high doses of haloperidol [8]. Like CATIE, the EUFEST study adopted all-cause treatment discontinuation at one year as primary endpoint, randomly assigning 498 subjects affected to haloperidol (n=103), amisulpride (n=104), olanzapine (n=105), quetiapine (n=104) or ziprasidone (n=82). The proportion of drug discontinuation was 72% for haloperidol, 40% for amisulpride, 33% for olanzapine and 53% for quetiapine. Thus, results showed that patients on low dose haloperidol had a greater treatment discontinuation at one year than patients on all of the second-generation antipsychotics. Moreover, global improvement as measured by CGI and GAF scale differed between treatment with most improvement recorded with amisulpride and least with quetiapine and haloperidol. On the other hand, symptom reductions, as measured by PANSS, and hospital admission rates did not show any difference. Those results led the authors to conclude that since discontinuation rates were not consistent with symptomatic improvement the superiority of second-generation antipsychotics versus haloperidol has not been confirmed [27].

Finally, two papers presenting data from CATIE and EUFEST reported no significant differences between FGAs and SGAs in terms of cognitive test performance [28, 29].

Clinical equipoise and the uncertainty principle

The concept of 'equipoise' holds that randomization is appropriate when there is substantial uncertainty as to which treatment is likely to provide greatest clinical benefit. This concept has been represented by many authors as a central ethical

principle of human experimentation [30-44]. As stated by Richard Ascroft: "It is widely maintained that a clinical trial is ethical only if some form of equipoise between the treatments being compared obtains. To be in equipoise between two treatments A and B is to be cognitively indifferent between the statement 'A is strictly more effective than B' and its negation ... Equipoise regarding A and B is necessary for randomized assignment to treatments A and B to be beneficent and non-maleficent and is sufficient for such an assignment to be fair" [30].

The ethical basis of equipoise has seldom been challenged. Surely physicians can ethically randomly assign patients to treatments if uncertainty exists. In this case, in fact, no trial participant would be given inferior treatment. However, some contrary considerations should be taken into account [45, 46]. Equipoise principle narrowly locates the ethical dilemma of human experimentation within the doctor-patient relationship [45]. In this framework, RCTs are subordinate to the delivery of optimal medical care and their value in developing new scientific knowledge is somewhat underrated. There is no definitive consensus on the boundaries of uncertainty, as its proponents have not yet clarified how to determine when it exists [45, 46]. An approximately 50-50 split in expert opinion is unlikely and, if literally interpreted, would substantially obstacle randomized clinical research. The reliance on expert opinion is another weak point of the classical formulation of the uncertainty principle [45]. The fact that the most rigorous approach to produce unbiased evidence should be allowed by mere expert opinion appears, in fact, somewhat contradictory.

These conflicting views suggest some caveats in the interpretation and application of the equipoise principle to RCTs. The reigning concept of equipoise makes no reference to the cost-effectiveness of treatments. Some new treatments could hardly justify their high costs in the light of their small advantages. On the other hand, the cost dimension could introduce significant levels of uncertainty in comparisons which otherwise would be considered unethical, thus generating rigorous knowledge to guide health policy

decisions [45]. Finally, equipoise promotes early discontinuation of RCTs based on interim data related to treatment benefit, and systematic reviews showed how the increasing incidence of these premature terminations could result in an overestimation of treatment benefits [47-49].

Clinical equipoise is a nuanced concept dependent on the existence of controversy about the relative value of two treatments being compared [50]. It should therefore not be literally interpreted. One possible reformulation of the equipoise principle in the context of RCTs has been proposed by Djulbegovic et al. (2000): "participants will not suffer relative harm from random assignment to a particular treatment arm; the results of a study cannot be predicted consistently in advance; and over a number of RCTs those proving or failing to prove an hypothesis will be approximately equal in number" [37].

Clinical equipoise, generally requires a trial design that will compare two treatments under the conditions in which they would be applied in practice and answer the question of which treatment should we prefer [51]. The observance of this principle should therefore be an important starting point in planning a phase IV, unblinded, pragmatic RCT. The aim of a pragmatic or effectiveness trial is to compare interventions within everyday clinical practice, and in this context no patient could be given inferior treatment. Moreover, as those trials deal with well-known therapies the existence of a state of clinical equipoise can be more clearly defined. Finally, the parameter of cost-effectiveness is usually taken into account in pragmatically defining the advantages or disadvantages of already marketed drugs.

If the ethical basis for planning a pragmatic trial should rely on equipoise, the ethical dilemma of whether to enter a patients in a randomized comparison refers to the so-called uncertainty principle [52]. This distinction has been made by some authors according to whom equipoise reflects a failure of general consensus within the clinical community whereas uncertainty reflects the personal belief of a single physician who

might be convinced that one treatment is better than another for a given patient. Uncertainty has been argued not to be a solid moral basis to opt for randomization. Under this subjective principle it would, in fact, be difficult to establish if a physician errs in excluding (or including) a patient from a trial [52]. However, uncertainty is an unavoidable prerequisite for randomization [53]. A responsible physician would hardly participate in an effectiveness trial if he or she is certain that one arm is superior to the others and that some of his or her patients will receive an inferior treatment by being randomized [52, 53].

Metabolic effects of new antipsychotics

Even if a better tolerability profile in terms of extrapyramidal side effects for SGAs has been recognized, an increasing number of reports concerning weight gain diabetes, ketoacidosis, hyperglycemia and lipid dysregulation in patients treated with SGAs have raised concerns about a possible association with metabolic effects [54, 55].

Metabolic syndrome is characterized by the combination of hyperinsulinaemia, low glucose tolerance, dyslipidaemia, hypertension, and abdominal obesity. This cluster has been recognized for many years, but the syndrome was not formally labelled until Reaven did so in 1988 and suggested that insulin resistance was its central characteristic [56]. Insulin resistance seems to be the main underlying factor leading to the increased risk of mortality from coronary heart disease among people with the syndrome. The clinical identification of metabolic syndrome is based on measures of abdominal obesity, atherogenic dyslipidaemia, hypertension, and glucose intolerance. The World Health Organization's definition of metabolic syndrome requires evidence of insulin resistance and measurement of fasting insulin or its surrogates as essential criteria [57]. The Adult Treatment Panel III of the US National Cholesterol Education Program (NCEP) , however, proposed a simpler definition, developed for clinical use and not including any estimation of insulin resistance [58, 59]. People meeting three of

the following criteria qualify as having the metabolic syndrome: high blood pressure (>130/85 mm Hg), low serum concentration of HDL cholesterol (<40 mg/dl in men or <50 mg/dl in women), high serum triglyceride concentration (≥150 mg/dl), high fasting plasma glucose concentration (≥110 mg/dl), and abdominal obesity (waist circumference >102 cm/40 inches in men and >88 cm/35 inches in women). A new definition, recently proposed by the International Diabetes Federation, has central obesity as an essential criterion, with a range of cut-offs for waist circumference for people from different ethnic groups [60]. Metabolic syndrome tends to evolve gradually and the presence of one or two features of the syndrome was found to be associated with increased risk of mortality from coronary heart disease and cardiovascular disease [61].

The prevalence of metabolic syndrome in the general adult population in developed countries is 22-39% and varies depending on the definition used and on ethnicity [62, 63]. Outcome data from the CATIE Schizophrenia Trial have provided important information on the metabolic and clinical impact of antipsychotic treatment for those subjects with metabolic syndrome and other medical comorbidities. Using baseline data, assessment of metabolic syndrome prevalence was performed based on NCEP criteria, and also using a fasting glucose threshold of 100 mg/dl (AHA) [64]. Among the 689 participants meeting inclusion criteria and applying both the NCEP and AHA derived criteria, the prevalence of metabolic syndrome was 40.9% and 42.7% respectively. In females it was 51.6% (NCEP) and 54.2% (AHA), compared to 36.0% ($p=0.0002$) and 36.6% ($p=0.0003$) in males respectively. 73.4% of all females (including non fasting subjects) met the waist circumference criterion compared to 36.6% of males. Comparative analyses were performed using a randomly selected sample from national general population estimates (NHANES III) [65]. In a logistic regression model with age, race and ethnicity as covariates, CATIE males were 138% more likely to have metabolic syndrome than the matched sample, and CATIE females

251% more likely than their counterparts. Even when controlling for differences in body mass index, CATIE males were still 85% more likely to have metabolic syndrome than the matched male sample, and CATIE females 137% more likely to have metabolic syndrome than females in the comparison group. Similarly, using baseline data from the same CATIE Trial, metabolic syndrome was found to be strongly associated with a poor self-rating of physical health and increased somatic preoccupation. There were no significant differences between the two groups on measures of symptom severity, depression, quality of life, cognition, or self-rated mental health. Neither years of antipsychotic exposure nor alcohol usage were significant predictors of metabolic syndrome status when adjusted for age, gender, race, and ethnicity [65].

Mortality in schizophrenia

There are extensive data linking people affected by schizophrenia or related psychosis to an elevated mortality risk [66]. Schizophrenic patients do not only have higher suicide rates but are at increased risk for premature death due to somatic conditions too [67]. Best available evidence shows that the differential mortality gap between people with schizophrenia and the general population has worsened in recent decades, with an almost linear increase in the standardized mortality ratio (SMR) from 1.84 in the '70s to 3.20 in the '90s [68]. This is somewhat inconsistent with the increased focus on comprehensive care and increase availability of treatment options for people affected by serious mental illness, which would have involved an improvement of life expectancy. Explanations for this increased mortality risk are complex and of multifactorial origin. Weight gain, smoking, poor diet and physical activity certainly play a significant role. Those risk factors are directly associated with the psychotic illness itself, as schizophrenic negative symptoms could be common underlying causes of most of these unhealthy behaviours. However, life-style or disease-specific risk factors

may not be sufficient to explain the entire differential mortality. In the last few years concern has grown about the well-known side-effects of antipsychotics and about the fact that they may have further contributed to shorten the lifespan of people with schizophrenia. Many FGAs and SGAs can cause significant weight gain, metabolic syndrome, diabetes mellitus, and cardiovascular disorders [54, 55, 66]. Moreover, evidence is accumulating linking antipsychotics to an increased risk of sudden cardiac death [69]. In fact, the prolongation of the QT interval induced by those drugs is advocated as one important causal mechanism for the ventricular tachyarrhythmias that often lead to sudden cardiac death. Weinmann et al. (2009) reviewed studies assessing the association between antipsychotic exposure and risk of death in schizophrenia concluding that although some evidence supports the hypothesis that long-term antipsychotic therapy may increase mortality, insufficient research attention has so far been devoted to this important issue [70].

All these results underline the need to take an active role in monitoring the physical health of patients with schizophrenia and to estimate the real impact of long term antipsychotic treatment on medical comorbidity and drug tolerability.

Indicators of cardiovascular risk

Cardiovascular diseases are among major threats to the future worldwide public health. Success in reducing cardiovascular mortality has been partially achieved. However, the aging of the population and the difficult reduction in risk factor prevalence will require more innovative approaches to predict and prevent major cardiovascular accidents. The metabolic syndrome is a constellation of closely related risk factors and represents a way of assimilating risk across the various pathogenetic pathways related to obesity [57-63]. Obesity is a major risk factor for cardiovascular disease, but the most predictive measure for different ethnic populations is still not clear. The World Health Organisation recognizes the body-mass index (BMI) as a universal criterion of

overweight (≥25) and obesity (≥30); measures of waist circumference (WC) or waist-to-hip ratio (WHR) are also encouraged [71]. Some authors have promoted anthropometric measures as good indicators of cardiovascular risk. WHR showed a graded and highly significant association with myocardial infarction risk resulting as stronger indicator than BMI [72]. Whereas, in a recent study testing the accuracy of anthropometric measures as indicators of metabolic syndrome, dyslipidemia and type 2 diabetes, WC and waist-to-height ratio (WHtR) were considered better predictors of cardiovascular risk [73]. In order to take into account the complexity of the pathogenesis of cardiovascular diseases some authors have created algorithms, scoring schemes and assessment tools to calculate individual risk. In particular, Sacco et al. (2009) proposed a global cardiovascular prediction tool incorporating traditional, anthropometric, and behavioural risk factors applicable to both white and non-white subjects which could improve primary prevention strategies [74].

2. Rationale

Independent funding

All these conflicting views called for the production of more independent and pragmatic evidence to guide clinicians in antipsychotic prescription. Therefore, the members of the Italian Group for the Study of Second-generation Antipsychotics (GiSAS) decided to design a pragmatic, open-label RCT aimed at comparing old and new antipsychotics in people with schizophrenia treated in routine Italian clinical settings. The Italian Group for the Study of Second-generation Antipsychotics was formed as a loose association in 2006 under the aegis of the 'Mario Negri' Institute for Pharmacological Research, a non-profit research institute dedicated to health sciences research. The group currently comprises 21 members all of whom are part of the GiSAS trial steering board.

The GiSAS group started working on the protocol and the Mario Negri Institute accepted to act as sponsor for the study. As it was not possible obtaining economical support from national public agencies, funding was ensured through an unrestricted grant from the drug company Bristol-Myers Squibb. The grant was accepted by the Mario Negri Institute on the basis of a contract that guarantees full independence and data property. Bristol-Myers Squibb had no direct involvement in the study design, in the collection, analysis and interpretation of the data.

The GiSAS trial was acknowledged by all the ethics committees involved as an independent study aimed at improving clinical practice in health care, according to the definition of the Italian Ministerial Act 17 December 2004. This national law recognizes the public health value of not-for-profit studies on clinically relevant topics. If certain specific and accountable criteria of independence are met, the National Health Service supports the study conduct, covering part of the expenses, like the costs of study

drugs and insurance. This allowed us to not rely only on industrial funding and to conduct a large multicenter study on a relatively low budget.

An independent review board has been set up to examine ethical issues related to the trial. All study data belong to the GiSAS trial investigators' group who undertake to publish them as soon as possible. Data will be analyzed and filed by the Laboratory of Epidemiology and Social Psychiatry of the Mario Negri Institute. Following publication of study results, full data will be made entirely available to the scientific community through unrestricted access to the trial database [75].

Choice of study drugs

All the above findings fuelled disagreement among researchers and clinicians instead of resolving the controversy about the comparative effectiveness of antipsychotic medications. This may be partly due to the fact that SGAs are not a homogeneous category, as they differ in many properties and comprise both old drugs, like clozapine and amisulpride, and the newer ones, such as aripiprazole and ziprasidone. The same can be said for FGA that also combine drugs with diverse side-effect profiles. In a recent critical review Leucht and colleagues concluded that although atypical antipsychotics are not a breakthrough, the overall evidence in favor of some of them is consistent. Thus, the debate for or against SGAs seems to be influenced more by values than by data [76].

Adverse reactions like metabolic disturbances or extrapyramidal symptoms are extremely common and somewhat class-specific effects of antipsychotic treatment [7-9]. Since the latest pragmatic RCTs were unable to settle the controversy on the comparative efficacy of SGAs over FGAs, we proposed a trial focused on tolerability. The purpose of the GiSAS study was to compare FGAs and SGAs in terms of tolerability and effectiveness with the goal of detecting clinically meaningful differences. We conceived the present trial to find out whether the

prescription of one of the selected antipsychotics would be associated with better treatment retention and would produce less harm than the others. The choice of study drugs was made taking into account tolerability and current prescribing practice in Italy and fell on three antipsychotics with different backgrounds and completely different tolerability profiles. Clozapine was excluded for its peculiar side-effect profile and difficult management [5, 6, 11]. Thus, among the other available SGAs (i.e. amisulpride, risperidone, olanzapine, quetiapine, and aripiprazole) we selected aripiprazole and olanzapine.

At the time the trial was being planned (2006) aripiprazole was the latest and most promising antipsychotic with a good but only preliminary reputation for tolerability (i.e. infrequent metabolic and extrapyramidal side-effects) and a still questioned reputation for effectiveness. The drug was approved by the FDA (USA) on the 15th November 2002, for the treatment of schizophrenia, and was later licensed also in Brazil (April 2003), Australia (May 2003), Swiss (July 2004), Japan (June 2006) and many other countries. Date of issue of marketing authorization valid throughout the European Union was 4 June 2004.

Aripiprazole was assumed to exert its antipsychotic effects by acting as a partial agonist at D2 dopamine- and 5-HT1a serotonin receptors, and as an antagonist at 5-HT2 serotonin receptors. In particular, it was postulated that, through the above receptor site actions, and hence dopamine and serotonin system stabilization, a partial D2 agonist would be able to act as an antagonist in pathways where an abundance of dopamine produces psychosis, and as an agonist at sites in which low dopaminergic tone would produce side effects (e.g. areas mediating motor movement and prolactin release) [77, 78]. Nevertheless, aripiprazole also has an affinity to other receptors including D3, D4, 5-HT2c, 5-HT7, alpha-1 adrenergic and H1 histamine receptors. This could explain adverse

effects associated with this compound such as sleepiness, headache, gastrointestinal upset and light-headedness [79].

A Cochrane systematic review of RCTs, first published in 2004, evaluated the effects of aripiprazole for people with schizophrenia and schizophrenia-like psychoses [80]. The reviewers searched the Cochrane Schizophrenia Group's Register (up to August 2004) and contacted relevant pharmaceutical companies, the FDA and authors of trials for additional information. All clinical randomised trials comparing aripiprazole with placebo, FGAs or SGAs for schizophrenia and schizophrenia-like psychoses were included. Despite the fact that 4125 people participated in 10 randomized studies, there were no usable data on number of death, general functioning, behavior, cognitive functioning, engagement with services, satisfaction with treatment and economic outcomes. Study attrition was very high and data reporting poor. Compared with FGAs, there were no significant benefits for aripiprazole with regards to global state, mental state, quality of life or leaving the study early. Both groups reported similar rates of adverse effects, including akathisia and general extrapyramidal effects. Aripiprazole, however, caused more insomnia than perphenazine and less need for anti-parkinsonian drugs than 10-20 mg/day haloperidol. When compared with olanzapine and risperidone, aripiprazole was neither better nor worse on outcomes of global state and leaving the study early, and adverse effect rates were also similar. On the whole, aripiprazole was associated with a low likelihood of inducing EPS, sedation, QTc prolongation, weight gain and metabolic abnormalities. However, evidence on its effectiveness and tolerability was still scant and its hypothesized different profile of therapeutic and adverse effects was not demonstrated [80].

Olanzapine is a widely used SGA and in the last years has been the most prescribed antipsychotic in Italy [81]. In the CATIE trial subjects receiving olanzapine showed greater effectiveness than the other agents despite its

association with significant metabolic disturbance, especially weight gain [82]; some commentators have pointed out that the doses of olanzapine were often higher than the upper limit of 20mg that may account for this better efficacy in the trial. On the whole, olanzapine had an excellent reputation for efficacy, and was known to cause few extrapyramidal symptoms; its use, however, was associated to well-known adverse effects on glucose and lipid metabolism [9, 54, 55].

Lastly, haloperidol was chosen being a highly potent and effective FGA and the most used comparator in clinical trials investigating the efficacy of antipsychotic drugs for schizophrenia [8, 14, 83-85]. In their review, Geddes and colleagues (2000) concluded that trials showing SGAs to be superior to haloperidol used too high doses of this drug [8]. It has so been argued that haloperidol's comparative effectiveness might improve with the adoption of a more prudent dosing approach, although this was not confirmed by most recent reviews [83, 85]. The use of haloperidol as control drug for randomized trials of new antipsychotics has been questioned for its propensity to cause extrapyramidal adverse-effects such as parkinsonism, akathisia and acute distonia [14, 83]. Movement disorders, however, were mostly associated with the prescription of high doses of haloperidol [14, 83, 84]. On the other hand, haloperidol has been associated with a low propensity to cause metabolic side effects, although this was never adequately investigated [84]. Haloperidol is the worldwide most prescribed FGA and is still widely prescribed in Italy, where a strong tradition of low-dosing may have led to a less critical view about its use [81].

In 2006 the above-mentioned Cochrane review on aripiprazole was updated by adding data of 2985 patients from 5 new papers but this did not significantly alter the main results or conclusions of the original review [80, 86]. Compared with FGAs there were no significant benefits for aripiprazole with regards to global

state, mental state, quality of life or leaving the study early. Both groups reported similar rates of adverse effects, with the exception of akathisia (n= 955 RR 0.31 CI 0.2 to 0.6, NNT 20 CI 17 to 32) and the need for antiparkinson medication (n=1854, 4 RCTs, RR 0.45 CI 0.3 to 0.6, NNT 4 CI 3 to 5) which were lower in those receiving aripiprazole. When compared with olanzapine and risperidone, aripiprazole was no better or worse on outcomes of global state and leaving the study early [86]. Two other recently published Cochrane reviews evaluated the effect of aripiprazole compared with FGAs [87] and SGAs [88]. Compared with typical antipsychotics, aripiprazole differed little in terms of efficacy but presented advantages in terms of tolerability [87]. It was associated with fewer extrapyramidal symptoms and hyperprolactinemia and with an advantage in terms of attrition rates. Compared with haloperidol, however, it did not show a significant advantage in terms of weight gain [87]. Compared with SGAs, aripiprazole resulted less efficacious than olanzapine, though only in terms of general mental state (PANSS score) and only in the short term [88]. It was associated with fewer side-effects like cholesterol increase, weight gain, sedation and prolactin associated problems. However, no differences were found in terms of leaving the studies early, cardiac effects, EPS and glycemia [88]. These findings are consistent with the meta-analysis already mentioned on metabolic side-effects of SGAs [13]. That review, in fact, found that aripiprazole was tolerated better than olanzapine in terms of weight gain and glucose and cholesterol elevation. Both analyses, however, were based on only two industry-sponsored RCTs and were biased by selective reporting [89, 90]. Even in the light of new evidence we can conclude that the planned comparisons are well-balanced and should produce innovative and clinically meaningful results.

Designing a trial within the pragmatic-explanatory continuum

The GiSAS trial was conceived to be large enough to identify small to moderate treatment effects differences and simple enough to be introduced in non-academic community mental health services (CMHS).

Peto et al. (1995) introduced the definition of "large, simple trial" which should be applied to randomized studies sufficiently powered to identify modest but clinically relevant effects and simple enough to allow easy participation of non-selected patients and providers [91]. More recently different terms, like "pragmatic" or "practical", were introduced to describe large and simple randomized clinical trials which should adopt sound and meaningful outcomes and include a range of heterogeneous practice settings and representative participants [18, 92]. Many authors considered those terms to be interchangeable. We opted for the appellation "pragmatic trial" because it echoed the empirical philosophy of pragmatism originated by the scientist Charles Peirce who argued that the importance of ideas or actions lies in whether they make a difference in everyday life and not only in their attractiveness [93, 94].

March et al. (2005) argued the case for practical clinical trials in psychiatry outlining their characteristics and scope [95]. Practical trials were characterized by the following defining principles: they should be randomized and performed in clinical practice settings; their questions should be simple and of substantial public health importance; their questions should belong to an important area of uncertainty; their outcomes should be sound, simple and clinically relevant; their procedures should enact best clinical practices and should minimize adjunctive burden to participants [95]. In mental health outcomes research the distinction is frequently made between efficacy and effectiveness trials or between explanatory versus pragmatic trials. Efficacy trials should ask the question: "Will a treatment work under ideal conditions?". On the contrary, effectiveness trials should ask:

"Will a treatment do more good than harm when implemented in everyday clinical practice?". Industry-funded registration trials represent the paradigmatic example of efficacy trials, whereas, quasi-experimental comparative research represents the far end of the effectiveness part of the spectrum [95].

The randomized clinical trial (RCT) has been developed as the gold standard for studies of treatment efficacy due to its potential for maximizing internal validity (i.e. the ability to attribute differential outcomes to the experimental manipulation of treatment rather than to other causes). Fundamental to this strength is the between-group equivalence produced by randomization, which permits the strong inference that alternative explanations can be eliminated [96]. Further, the rigorous controls and standardization characteristic of RCTs (i.e. blinding and concealment) reduce variability in both treatment delivery and outcome measurement, thereby enhancing the statistical power to detect treatment effects. From this point of view, pragmatic trials represent an evolution in the direction of enhancing the external validity of experimental design (i.e. the generalizability of the results).

All the above mentioned definitions mostly refer to a trial's purpose. However, the degree to which the purpose is met depends on how the trial is specifically designed and conducted. Moreover, few trials are completely pragmatic or explanatory and most of them find their place on a continuum. Currently no validated definition of effectiveness studies exist. Therefore, standardized tools to assess and display the position of a given trial within the pragmatic-explanatory spectrum have been recently proposed [97, 98].

The GiSAS trial was designed to be conducted in a representative group of Italian CMHS which are the first care facilities available to the general population. The purpose was to develop a pragmatic randomized study to test the effectiveness and tolerability of three antipsychotic drugs in the medium and long-term

treatment of schizophrenia. Therefore, the following pragmatic features have been adopted: wide eligibility criteria to promote participation of a wide range of subjects with the condition of interest; flexibility of experimental interventions and of follow-up assessments; objectively measured and clinically relevant outcomes; unobtrusive measurement of participant compliance to study intervention or practitioner adherence to study protocol; full intention-to-treat (ITT) analysis of primary outcome [98]. The study was planned to include an experimental treatment phase (randomized study) and an observational follow-up phase (cohort study).

3. Methods

Aim

Given the unsettled controversy on the comparative efficacy of first- over second-generation antipsychotics, clinicians should face a substantial uncertainty in the choice of the antipsychotic likely to provide greatest clinical benefit in adult patients with no specific counter-indications who responded insufficiently to antipsychotic medications. The aim of the trial was to compare the medium- and long-term tolerability and effectiveness of aripiprazole, olanzapine and haloperidol in schizophrenic patients without diabetes or metabolic syndrome and who had been already exposed to antipsychotic drugs. The onset of metabolic syndrome and the occurrence of drug discontinuation at one year were adopted as main outcome indicators.

Study design

The GiSAS trial is an open label, one-year randomized controlled trial firmly rooted in everyday clinical practice. To enhance representativeness, the inclusion criteria were wide and recruitment takes place in a broad array of clinical settings and across the various components of service provision. The sample was meant to be heterogeneous and to reflect the real population attending Italian community psychiatric services, recruiting a broad range of "real-world" patients, including those with comorbid conditions (i.e. substance use disorders, medical problems). In a non-selected sample of schizophrenic patients, it was hypothesized that there were significant differences in the overall safety, tolerability and acceptability of aripirazole, olanzapine and haloperidol and consequently in their effectiveness.

Eligible subjects were randomly assigned to non-blind oral monotherapy with one of the study drugs. Principal investigators and data analysts were blinded, but

clinicians and patients knew the allocated treatment. The study was not designed to replace any aspect of the usual clinical care. During follow-up, the participants were seen as often as usually clinically indicated. For each patient, all examinations were performed in the respective recruiting center by the designed clinician.

Patients were assessed:

- at baseline (all subjects);
- when monotherapy treatment is stopped or changed (those who stop);
- at 12 months (all subjects).

At the end of the 12-month follow-up period, all randomized patients entered a 2-years prospective observational study.

All the study procedures are described in the Manual of Procedures (see APPENDIX 1) and in the Monitoring Manual (available in Italian).

Sample selection

Inclusion criteria:

- Age 18 years and over.
- DSM-IV diagnosis of schizophrenia, based on the Mini International Neuropsychiatric Interview [99].
- patients entering the study should, according to their own judgment and in consultation with their doctor, have had a condition appropriate for changing current antipsychotic treatment.

The latter criterion represents the crucial starting point of the trial. Patients should have been included in the study only if the current medication is somehow unsatisfactory. However, subjects already taking one of the study drugs at study entry

were not excluded. Thus, given the possibility not to change medication, staying on the same antipsychotic must have been considered a viable clinical option.

Exclusion criteria:

- Diagnosis of metabolic syndrome, defined as the fulfilling of at least three of the diagnostic criteria for the metabolic syndrome derived from Adult Treatment Protocol III (ATP III) [59]:
    1. Abdominal obesity (waist circumference >102 cm in men and >88 cm in women);
    2. Fasting triglycerides (Tg) ≥150 mg/dl;
    3. High Density Lipoprotein (HDL) <40 mg/dl in men or <50 mg/dl in women;
    4. High blood pressure ≥130/85 mm Hg or on antihypertensive medication;
    5. Fasting glucose ≥110 mg/dl or on insulin or hypoglycemic medication.
- Diagnosis of diabetes mellitus type II.
- Any organic condition clearly contraindicating treatment with one of the studied drugs (e.g. pregnancy or breast-feeding).
- Known ineffectiveness or intolerance of one of the study drugs, which was consequently contraindicated.
- The patient had never been exposed to antipsychotic drugs.
- According to clinician's opinion, it was unlikely that the patient could have been followed-up for the whole duration of the study (one year).

Recruitment

The principle of uncertainty, which has been proposed by many authors as the cornerstone of the credibility of a clinical trial, was adopted as the leading criterion for GiSAS recruitment [52, 53]. A subject should have been excluded from the trial if one of the three study drugs had already proven ineffective or intolerable or if the treating clinician had some definite idea of which antipsychotic would fit best.

Recruitment was conducted in a broad array of community settings: outpatient clinics, acute hospital units, residential facilities and day centers. Patients meeting the inclusion criteria were asked to participate and, after giving informed consent, could access randomization (see APPENDIX 2: Recruitment Form). Once randomized, subjects were included in the study if they took at least one dose of the assigned medication. The recruitment forms of the excluded subjects were filed and periodically reconsidered for inclusion.

Baseline assessment

For those who consented to participate the following information were collected at baseline:

- clinical and demographic characteristics;
- vital signs (ECG, arterial pressure and pulse frequency);
- anthropometric measures (WC; WHR; WHtR);
- standard clinical laboratory test (hemochrome, electrolytes) and serum lipid profile, glycemia, prolactinemia;
- pharmacological treatments;
- psychiatric symptoms: Brief Psychiatric Rating Scale 4.0 [100];
- side effects induced by previous antipsychotic treatments;
- Patients' subjective reports of antipsychotic adverse effects, assessed by the Liverpool University Neuroleptic Side Effect Rating Scale (LUNSERS) [101];
- global assessment of functioning (GAF) [102].

Psychopathology was measured by the Brief Psychiatric Rating Scale 4.0 (BPRS) [100]. The BPRS consists of 24 items rated on a seven-point Likert scale (1=no symptom; 7=extremely severe symptom). Items cover four dimensions: anxiety/depression (constituted by six items: somatic concern, anxiety, depression, suicidality, guilt,

tension); positive symptoms (five items: grandiosity, suspiciousness, hallucinations, unusual thought content, conceptual disorganisation); negative symptoms (seven items: blunted affect, emotional withdrawal, motor retardation, uncooperativeness, self-neglect, disorientation, mannerisms); and mania (hostility, elevated mood, bizarre behaviour, self-neglect, uncooperativeness, excitement, distractibility, motor hyperactivity, mannerisms).

Patients' subjective reports of adverse antipsychotic effects were measured by the Liverpool University Neuroleptic Side Effect Rating Scale (LUNSERS) [101]. The LUNSERS is a 51-item, self-rating scale. Respondent are required to indicate how much in the previous month they have experienced each of the adverse effects listed with regard to 41 known side effects and 10 "red herring" symptoms not known to be side effects of antipsychotic medication. Responses are scored on a five-point scale: 0 = not at all; 1 = very little; 2 = a little; 3 = quite a lot; 4 = very much. Different subgroups of adverse effects could be obtained from the scale: extrapyramidal reactions (7 items), anticholinergic reactions (5 items), other autonomic reactions (5 items), allergic reactions (5 items), physic reactions (10 items), endocrine reactions (6 items), other reactions (4 items).

The Global Assessment of Functioning Scale (GAF) is a well known rating scale, scoring 1-100, which can be found as Axis V of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) [102]. It covers the range from exceptionally good mental health and functioning to severe psychopathology. It measures the severity of mental illness taking into account psychological, social and occupational functioning as well as symptoms. It is a global and comprehensive measure of how patients are getting along in their current situation, and is intended to be a generic rather than a diagnosis-specific scoring system. The 100-point scales are divided into intervals, or sections, each with 10 points (for example 31-40 and 51-60). The scale is provided with examples of what should be scored in each 10-point interval. Written instructions

describing hierarchies of relevant symptoms and functional impairment (anchor points) are provided. For interval 1-10 the anchor points describe the most severely ill, for interval 91-100 describe the healthiest. The finer grading within intervals provides the possibility of distinguishing between nuances, but there are no written instructions for this.

All baseline data were recorded in the **Baseline Form (BF)** (see APPENDIX 3).

Randomization

Eligible patients were randomized to the three treatment arms following a 1:1:1 procedure. Randomization was stratified by site. Although the number of criteria already satisfied in a patient at study entry could be a powerful predictor of developing metabolic syndrome at follow-up, the low number of subjects recruited per center made it impossible to stratify also for this variable. The analysis of the primary outcome will be adjusted for the number of criteria already met at study entry

The allocation sequence (computer generated random-sequence) was registered before the trial's start. Investigators were unaware of the exact details of how the chosen randomization method was being implemented.

A central randomization by telephone with an interactive voice response system was adopted. Investigators assessed eligibility, gaint consent, and made the decision to enroll a patient at the participating site, then called the randomization service to get the treatment allocation and the subject's code. All records on the randomization database (e.g. failed calls, unregistered randomizations) were monitored to detect attempts to decipher allocation.

Masking

Those who are directly involved in patients' care were not blinded. In blinded trials clinicians are not in condition to tune and adjust the optimal dose to the individual patients. The open-label nature of this trial enhances its feasibility, reflects real clinical practice, increases its external validity and consequently the generalizability of the results. However, knowing to which drug a subject has been assigned could theoretically influence outcome thus decreasing the internal validity of the comparison and the strength of the inference [96]. To explore the possible effect of clinicians expectations on outcome, investigators' attitude towards the study drugs has been surveyed (see below: GiSAS survey).

Post-randomization exclusion represents another critical issue related to the open nature of treatment allocation. To avoid this, adherence to the best possible standards of trial execution has been constantly supported by trial management. Through the weekly monitoring of the randomization database clinicians were actively prompted to prescribe the allocated drug. At this stage, dropping out of the trial was not an easy option for the clinician and was considered acceptable only if patients withdrew informed consent.

All people involved in GiSAS trial coordination, supervision, and data analysis were blinded.

Study medications

At study start-up all the study drugs were already licensed and marketed in Italy for the treatment of schizophrenia [103]. After randomization, the assigned daily oral doses of the assigned drugs was prescribed according to usual care practice and adjusted according to individual response and side effects

Although clinicians were not constrained to follow strict dose ranges, suggested doses are as follows:

- Aripiprazole 10 mg/day starting dose and 10-30 mg/day dose range.
- Olanzapine 5 mg/day starting dose and 10-20 mg/day dose range.
- Haloperidol 1-3 mg/day starting dose and 3-10 mg/day dose range.

For patients already taking an antipsychotic medication prior to study entry, tapering the previous medication over a period of at least four weeks was suggested. Guidelines have been provided in order to allow physicians to choose the switching strategy which is the best for the patients and with which they are most comfortable. The use of concomitant antipsychotic medication at the end of the switch period was considered as a discontinuation of the allocated drug.

Participation in another pharmacological trial is prohibited.

All these data were recorded in the **Treatment Form** (**TF**) (see APPENDIX 4).

Concomitant medications

After inclusion no limits have been imposed to the clinicians who were free to treat patients at their own discretion. The only exception was represented by mood stabilizers, being their use associated with the onset of metabolic disturbances [104]. The prescription of mood stabilizers is allowed only for subjects who were on these medications prior to study entry. On the contrary, the subsequent prescription of mood stabilizers is to be considered a protocol violation.

The prescription of concomitant antipsychotic therapy was allowed but considered treatment failure. The occasional occurring of parenteral antipsychotic drug administration (i.e., during emergency admission) was not allowed. A temporary stop of the assigned antipsychotic (no longer than 2 weeks in 6 months) was not considered as drug discontinuation, thus was not considered as a reason to perform a follow-up assessment.

The use of concomitant psychotropic medication (e.g. benzodiazepines, antidepressants) or of non-psychotropic drugs (e.g. anticholinergic drugs, beta-blockers, statins) was allowed and routinely recorded. Data on their prescription will be used in the secondary analyses.

All these data were recorded in the **Treatment Form** (**TF**) (see APPENDIX 4).

Primary outcomes

The onset of metabolic syndrome was adopted as primary negative endpoint. The study design and conduction, however, are focused on drug retention and the study power has been estimated for this endpoint too. Thus, the trial takes account of two primary endpoints: one for tolerability and one for effectiveness. Together, in fact, they must provide the most clinically relevant and convincing evidence directly related to the primary objective of the trial.

Do not develop metabolic syndrome after a one-year trial of antipsychotic was considered treatment success. The onset of metabolic syndrome, defined by meeting at least three of the above mentioned criteria, was considered as treatment failure even for patients with one or two clinical signs of metabolic syndrome at study entry.

The onset of metabolic syndrome was recorded at the end of the trial or when the assigned monotherapy treatment was stopped/changed or a second antipsychotic was added. Analyses were centralized and assessment of metabolic syndrome parameters were performed in the same reference laboratory.

All-cause discontinuation of the allocated drug monotherapy during follow-up were considered treatment failure. Treatment discontinuation is a discrete measure of effectiveness that, being the result of intolerable side effects, insufficient clinical effect or inconstant acceptance or compliance, could reflect both tolerability and efficacy.

Switching to another antipsychotic, adding a second antipsychotic or stopping the assigned drug was classified as study drug discontinuation. Reasons for discontinuing the assigned antipsychotic was registered in the TF but not considered in the primary outcome (see Figure 1).

Patients who meet the criteria for drug discontinuation were counted as treatment failures with regard to effectiveness but were followed-up for the rest of the one-year period as well.

In order to capture whether, when and why participants stopped the assigned treatment or added concomitant medication the patients' ongoing treatments was strictly monitored. The occasional occurring of parenteral antipsychotic drug administration (i.e. during emergency admission,) was allowed. A temporary stop of the assigned antipsychotic (no longer than two weeks in six months) was not considered as drug discontinuation.

The proportion of subjects who will discontinue treatment during the 12-months follow-up will be compared between the three study groups. Time to discontinuation will be taken into account in the secondary analysis.

DRUG DISCONTINUATION MODULE

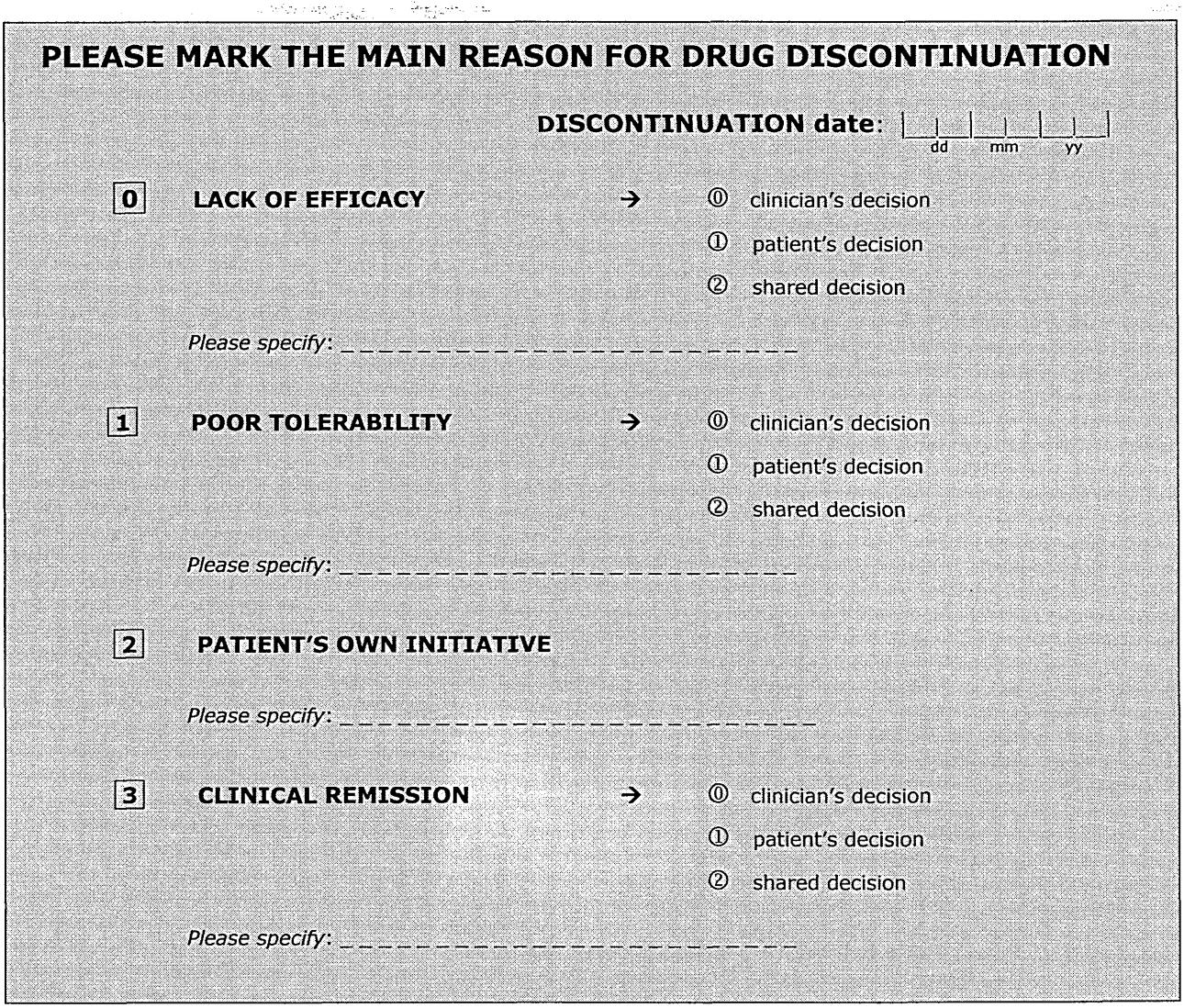


Fig. 1. The study drug discontinuation module in the trial monitoring form.

Secondary outcomes

The following secondary endpoints were taken into account:

- reasons for study drug discontinuation;
- Global Assessment of Functioning score [102];
- worsening of metabolic profile, defined as the new onset of at least one metabolic syndrome criterion;
- onset of serum lipids abnormalities (dyslipidemia);
- waist-to-hip-ratio (WHR);
- electrocardiographic abnormalities;
- hyperprolactinemia (reference ranges for prolactin are 3.57 to 12.78 ng/mL for men and 6.12 to 30.54 ng/mL for women);
- onset of extrapyramidal side effects, derived from from antiparkinson drugs use;
- Concurrent use of psychotropic medication, to pragmatically evaluate the occurrence of further psychiatric symptoms or changes in different dimensions of psychopathology;
- Patients' subjective assessment of adverse effects, assessed by LUNSERS [101].

Follow-up evaluations

Included subjects were assessed (a) at baseline, (b) when monotherapy treatment was stopped or changed and (c) at 12 months. Thus, at the end of the trial all subjects were re-assessed even if they have stopped or changed the assigned drug.

During the one-year follow-up period, the participants have been seen as often as usually clinically indicated (about once a month). On these occasions investigators were asked to fill a specific monitoring form to check if any change in the patient's medication has occurred (TF).

With the exception of the centralized analyses, which were performed by 'Mario Negri' Institute to detect metabolic disturbances, for each patient all examinations were carried out by the designed clinician in the respective recruiting centre. Any psychosocial intervention provided by services all along the study period was monitored and recorded.

All follow-up data were recorded in the **Follow-up Form** (**FF**) (see APPENDIX 5).

Data analysis

All analyses will be by full intention-to-treat (ITT) including all randomized participants who will receive at least one dose of investigational drugs. Subjects already taking one of the study drugs at study entry could never be excluded from the ITT analysis.

Analyses will be performed on both the full ITT population (i.e. all randomized participants) and the modified ITT population (i.e. randomized participants receiving at least one drug dose).

Collected data will be analyzed using a last-observation-carried-forward approach. Patients with no follow-up data available will be allocated to the outcome category of treatment failure.

The proportion of participants in each treatment arm who developed metabolic syndrome at follow-up was adopted as primary endpoint for tolerability. At baseline subjects could meet up to two metabolic syndrome criteria. A statistical analysis of the primary outcome will adjust for the number of criteria already met at study entry.

The proportion of patients who maintained the allocated antipsychotic treatment as a monotherapy in each treatment arm within a year was adopted as primary endpoint for effectiveness.

Mean GAF scores in each treatment arm will be compared. Covariance analysis and effect size calculation will be performed.

Survival analysis of time to discontinuation due to treatment-related side effects will be carried out. Subgroup comparisons will be performed to analyze subjects who stopped treatment due to (a) extrapyramidal side effects, (b) onset of metabolic syndrome. Moreover, the proportion of patients whose metabolic profile worsened at follow-up will be taken into account. The proportion of normolipidemic/dislipidemic participants in each treatment arm at follow-up was evaluated. Participants will be divided into two groups according to their lipid profile at study entry and the two groups will be analyzed separately

Mean waist-to-hip-ratio in each treatment arm will be compared. Covariance analysis and effect size calculation will be performed.

Mean LUNSERS scores in each treatment arm will be compared. Covariance analysis and effect size calculation will be performed.

The proportion of patients developing electrocardiographic abnormalities in each treatment arm will be compared (see FF: APPENDIX 5).

The proportion of patients in each treatment arm who will take antiparkinson drugs or adjunctive psychotropic medication will be used to pragmatically evaluate the onset of extrapyramidal symptoms or the occurrence of further psychiatric symptoms.

Statistical analysis

The main goal of the trial is to test the null hypothesis that the proportion of cases developing metabolic syndrome is equivalent for all three drugs. The criterion for significance (alpha) has been set at 0.05 (2-tailed). Treatments will be compared by use of a logistic regression model taking into account the stratification criterion used (trial site).

For all statistical analyses, sites with a small number of randomized patients will be pooled together. The analyses will be conducted on the intention-to-treat population: all subjects who take at least one dose of study medication will be included.

If the null hypothesis of the three treatments being equal is rejected, subsequent analyses will be performed considering each pair of drugs.

Pairwise comparisons between the three treatments will be carried out ensuring that the overall Type I error rate is maintained at 0.05 using a Hochberg adjustment for multiple comparisons. All three comparisons will be significant if the largest p-value will be ≤ 0.05, the two strongest comparisons will be significant if the second smallest p-value will be ≤ 0.025, and only the strongest comparison will be significant if the smallest p-value will be ≤ 0.0167.

As secondary steps, survival analyses using Cox Proportional Hazards regression models and logistic regressions/analyses of covariance will be used on the secondary outcome measures. In survival analyses, subjects still on treatment one year after randomization will be censored.

The study power was calculated as follows. The criteria for significance were set at 0.05 (2-tailed), corrected for multiple testing, wherever necessary.On the basis of data extrapolated from recent studies [16, 72-75], it was hypothesized that the percentage of patients who will develop metabolic syndrome within 12 months will be 25% in the group treated with olanzapine, 15% in the group treated with haloperidol and 5% in the aripiprazole group.

The first step of the primary analysis was an overall 2 degree of freedom test (using a 2 df Chi square as an approximation for the logistic regression). The proposed total sample size of 750 subjects (see below for discussion of the number) had power exceeding 99% to yield a statistically significant result. If a significant difference was found, pairwise comparisons between the study drugs were be evaluated. To detect

significant differences within each single comparison, an increase of the statistical power was required.

Assuming that (a) the smallest detectable difference was to be found in the olanzapine vs. haloperidol comparison (to be found at p=0.05), (b) the second smallest difference would be found in the haloperidol versus aripiprazole (at p=0.025), and (c) the highest difference found in the aripiprazole and olanzapine comparison (at p=0.016), 250 subjects per group were calculated to correspond to a power of, respectively, 80%, 93% and more than 99%. If the percentage of patients on aripiprazole developing a metabolic syndrome were 7%, the power to detect a difference against a 15% on haloperidol was be 73%.

To protect against a possible drop-out rate of 5-10%, about 800 patients were required for the study.

On the basis of data extrapolated from the most recent and comparable study [16], it was hypothesised that retention at 12 months would be 45% in the group treated with olanzapine, and 30% in the group treated with haloperidol. We assumed a retention rate of 60% in the group treated with aripiprazole. Using the above calculated sample size (n=800), the measure of effectiveness adopted as secondary outcome (retention rate at one year) had a power >85% to detect significant differences (alpha=0.05/0.025/0.016, 2-tailed) between the three possible pairwise comparisons using a logistic regression.

As patient recruitment to the GiSAS trial was a serious problem (see below: Trial planning and conduct) the originally hypothesized sample size could not be achieved. Thus, we opted to downsize the sample to about one-third of the original size. Adjustment for multiple comparisons lowers statistical power. Therefore, to preserve the study power we chose to cut one of the planned comparisons and to focus on aripiprazole vs. olanzapine, and aripiprazole vs. haloperidol. The less original comparison between olanzapine and haloperidol was moved to the secondary analyses.

We predicted to recruit about 250 subjects. Assuming that drop-out rate will be marginal (less than 5%) data from 240 subjects should be available for analyses.

The first step of the primary analysis is an overall 2 degree of freedom test (using a 2 df Chi square as an approximation for the logistic regression). The proposed total sample size of 240 subjects will have a power of 89% to yield a statistically significant result. If a significant difference is found, pairwise comparisons between the aripiprazole and the two other compounds will be performed. Assuming that (a) the smallest detectable difference is found in the aripiprazole (5%) vs. haloperidol (20%) comparison (to be found at p=0.05), and (b) the largest difference is found in the aripiprazole (5%) vs. olanzapine (25%) (at p=0.025), 80 subjects per group will correspond to a power of, respectively, 77% and 87%.

Data ownership

All study data belong to the GISAS Trial investigators group. Data collected for this study will be analyzed by the Istituto di Ricerche Farmacologiche "Mario Negri" in Milan.

Following the publication of study results, data will made available for the scientific community.

Cohort study

At the end of the 12-month follow-up period, all randomized patients who gave their consent entered a prospective observational study. Participants were evaluated every six month for the subsequent 2 years using the above mentioned TF and FF.

Pharmacogenetic study

All randomized patients who gave specific informed consent entered a pharmacogenetic ancillary study. Genetic samples were collected at each study site and processed at the study coordination centre (the Laboratory of Genetics, Galliera Hospital, Genova).

A candidate gene approach will be used. Thus, genes will be selected from current evidence and their association with drug response will be investigated. The same endpoints adopted in the present trial will be used to define treatment response. No further data will be collected.

Publications

The primary publication from GISAS Trial will be attributed to the GISAS Study Group. The names of all investigators who randomize patients within the trial will be listed with the Principal Investigators and Steering Group at the end of the primary publication. Subsequent publications will be permitted after approval from the GISAS Trial Scientific Advisory Board.

4. Trial design considerations

Two primary endpoints?

The ICH E9 guideline on biostatistics in clinical trials states that safety/tolerability may sometimes be the primary variable, and will always be an important consideration [105]. As metabolic disturbances or EPS are extremely common negative consequences of antipsychotic treatment, Tyrer and Kendall (2008) wrote that serious adverse reactions should be adopted as important outcome measures [106]. The decision to focus on tolerability and to adopt a harmful effect as primary –negative– outcome, although uncommon, could therefore be valuable for improving the pharmacological treatment of schizophrenia. Endpoints selected for clinical trials must strike a balance between their scientific validity and their practical and clinical importance. Since metabolic side-effects of SGAs (i.e. weight gain, dyslipidemia and impaired fasting glucose) were emerging issues and since aripiprazole showed an at least promising metabolic profile we chose as primary endpoint for tolerability the incidence of metabolic syndrome.

According to the ICH E9 guideline, we indicated one primary variable as primary endpoint [105]. However, as the study design and conduction focused on drug retention, we took also account of drug discontinuation as endpoint of primary importance. Both endpoints were used to estimate the sample size because together they should provide the most clinically important and convincing evidence directly related to the primary objective of the trial [107].

Previous antipsychotic medication

Patients who were on antipsychotic therapy at study entry should have had a condition appropriate for changing their treatment to be considered for inclusion. This criterion

was the natural starting point of the trial: patients should have been randomized only if the current medication was somehow unsatisfactory. A trial recruiting subjects with severe, long-lasting disorders has to deal with previous and current pharmacological treatments. As in CATIE we decided to allow random assignment to the medication taken prior to study entry. Given the possibility of not changing medication, staying on the same antipsychotic had to be a viable clinical option. On the other hand, those who were completely satisfied with their medication would have not been entered into the study. Therefore, GiSAS participants who at baseline were already taking olanzapine, haloperidol or aripiprazole should have not been completely satisfied with their medication but did not need absolutely to change it. The use of the ITT principle allowed us to preserve randomization from any subsequent change of the allocated drug. Thus, if continuing previous medication turned out to be the wrong choice clinicians could easily intervene without affecting trial participation.

In CATIE phase I, 23% of subjects randomly assigned to olanzapine and 18% of subjects randomly assigned to risperidone did not change medication because they already were on those drugs at study entry. In a post-hoc study, Essock and colleagues (2006) found that those "stayers" had significantly longer times until discontinuation than those assigned to switch, and that, when these "stayers" were removed, differences seen in the original CATIE results were attenuated [108]. As exposure to treatment prior to the trial seemed to advantage "stayers", the authors concluded that future randomized comparisons should take into account whether medications being compared were newly initiated or not [108]. In a subsequent study a similar analysis addressing additional outcomes measures evaluating symptoms, neurocognition, quality of life, neurological side effects, weight, and health costs was performed [109]. Switching to a new medication yielded no advantage over staying on the previous medication. However, staying on olanzapine was associated with greater weight gain [109]. These analyses showed that, even in double-blind RCTs, there can

be biases in treatment effect estimates related to differences in the study participants' previous exposures to treatment. Comparisons of medication effectiveness need to take into account whether medications being compared were each newly initiated. We will take into consideration this potential source of bias adjusting for being "stayers" both primary endpoints.

Potential sources of bias

Some characteristics of the study design might be sources of bias. Patients and their treating psychiatrists were unmasked for the assigned treatment, since this better reflects routine clinical practice increasing the trial's external validity. Knowledge of the treatment allocation and drug prescribed, however, can influence the referring clinician's and participant's assessment and interpretation of effectiveness and side-effects, and this might in turn influence treatment decisions and patients' subsequent use of the service and outcomes. The only strategy we could adopt to compensate this bias was to survey clinicians' attitudes towards antipsychotics with the aim of using these data to control for possible confounders (see below: GiSAS Survey). A secondary statistical analysis of the primary outcomes will adjust for clinicians' expectations of the effectiveness and tolerability of the various antipsychotic classes.

Post-randomization exclusion is another problematic issue related to the open nature of the trial. We decided to include in the modified-ITT analysis only patients who had taken at least one dose of study medication. Thus, since patients and their psychiatrists were unblinded, they could choose to opt out of the trial if their treatment did not turn out to be the one they wanted. To deal with this, investigators were always prompted to adhere to the best possible standards of trial execution. All records on the randomization database (e.g. failed calls, unregistered and registered randomizations) are monitored by the study team on a weekly basis in order to detect any attempts to decipher allocation and to actively prompt clinicians to prescribe the

allocated drug. At this stage, dropping out of the trial is not an easy option for the clinician and is considered acceptable only if patients withdraw informed consent. Moreover, patients for whom the allocated treatment turns out to be the same cannot be excluded from the modified-ITT analysis since, by definition, they have already taken at least one dose of the investigational drug. I wish to clarify that the inclusion in the modified-ITT analysis was not only determined by the actual intake of the assigned drug. No specific way of controlling patients' compliance was prescribed, thus inclusion was not determined by treatment adherence. To fulfil our inclusion criteria the allocated drug should simply have been directly prescribed to the patient by the treating clinician in a face-to-face meeting. If this has happened the patient qualifies for inclusion. The basic ITT principle is that participants should be analyzed in the groups to which they were randomized, regardless of whether they received or adhered to the allocated intervention and regardless of whether they withdrew from the trial. Nevertheless, we decided to link patients' inclusion to the prescription of the allocated treatment and not simply to randomization. This allowed us to maintain a certain control over the inclusion phase and to obtain that the allocated drugs were actually prescribed. Had we not done so, investigators would have probably considered randomization only as a feeble suggestion and many subjects would have been prescribed different treatments.

Conclusion

The protocol of a pragmatic clinical trial should be as simple as possible. Its design should attempt to mirror routine clinical practice, as in this context are the study hypotheses to be tested. This is aimed at increasing the trial's feasibility and the possibility that its results will have a significant impact on the clinical community.

The GiSAS trial was projected as a community effectiveness randomized controlled trial. Therefore, its procedures, while promoting best available practices without giving

inferior treatment to any participant, had to match with the everyday clinical practice of Italian community mental health services. Some of the difficulties encountered in the trial implementation (see below) might be interpreted as an effect of this compromise. The fact of allowing randomization only when the clinicians were really uncertain about the drug choice could have paved the way for a significant slowdown of recruitment. On the other hand, the attempt to mimic everyday clinical practice conflicted with the random assignment of medication or with the fixed prescription of blood and electrocardiographic examinations.

CHAPTER II

TRIAL PLANNING AND CONDUCT

5. Trial conduct and patient recruitment

The study protocol, the study manual, the information brochure and the informed consent form have been approved by the ethics research review board of the clinical coordinating center, the Local Health Agency of Genoa (n° 49549, March 2007). The trial has been approved as an independent study aimed at improving clinical practice in health care, according to the definition of the Italian Ministerial Act 17 December 2004, and has been registered in the National Monitoring Centre for Clinical Trials and the European Clinical Trial Database (EudraCT number 2007-000278-22) and in the ClinicalTrials.gov registry (number NCT01052389) [110, 111]. The approval was released on 15 March 2007 and transmitted to the principal investigator Dr. Luigi Ferrannini, director of the local Mental Health Department, to the study sponsor, the 'Mario Negri' Institute for Pharmacological Research, and to the National Monitoring Centre for Clinical Trials (https://oss-sper-clin.agenziafarmaco.it/index_ingl.htm). Local research ethics review boards approval has been obtained for each participating center.

In Italy, this is one of the first attempts to apply the model of "pragmatic trials" in the field of antipsychotic treatment. The study is coordinated by the Epidemiology and Social Psychiatry Unit of the Mario Negri Institute for Pharmacological Research in collaboration with the Department of Mental Health of the Local Health Agency of Genoa and the Department of Psychiatry of the University of L'Aquila.

All study sites were monitored on a regular basis, case record forms checked and data entered in the central database. According to Good Clinical Practice, all necessary procedures to ensure the quality of every aspect of the trial are complied with. Patient information is only accessible to the research team and no identifying information is kept with raw data. Each study investigator keeps records of laboratory tests and ECG diagrams in the patient's file as original source documents for the study.

Two protocol amendments were submitted to all ethics committees and approved within the first three years of study implementation: a) the recruitment period, which was estimated at one year for each study center (see APPENDIX 1), was prolonged; b) the sample size was downsized to about one-third of the original size (see above: paragraph *3.14.1*).

All phases of the GiSAS trial are recorded following the CONSORT statement [112].

Recruitment initiatives

In the early phase of recruitment, conferences at each participating Units have been held to present the overall profile of the project.

Once the local ethics committees approved the protocol, further meetings were scheduled in order to give detailed information and practical advice on patients' screening and inclusion. Raising suitable and well-motivated clinicians became the focus of start-up phase of the study.

Participating centers and sample recruitment (updated June 2011)

48 centres across Italy were initially involved. Three centres (6%) withdrew before ethics approval was complete. Three local research ethics review boards (6%) did not approve the study. After participation agreement and ethical approval two centres (4%) withdrew from the study for reasons of time constraints and work overload and five centres (10%) failed to recruit any patients.

The 35 participating centers, all belonging to the National Health Service (SSN) are listed in Table 2. Most of them have taken a long time before becoming operative and only 16 of them (46%) reached the original recruitment target of at least 10 subjects per center.

The study recruitment from October 2007 to June 2008 was very problematic. Patient inclusion was very low in the first nine months of recruitment: only 34 subjects had been randomized by June 2008 (see Figure 2 for details). Table 3 shows data on the screening and inclusion of patients carried out by GiSAS investigators between October 2007 and June 2009 at 8 study sites (17 recruiting centers). Figure 3 shows CONSORT flow-chart of the first 34 recruited subjects (June 2008).There was a huge variation across the sites in the proportion between patients screened for eligibility and patients included in the study: from 0.02 in Piacenza to 1 in Rho or Savona. Screening

procedures had been applied differently despite all our efforts to uniform inclusion across the trial centres. Figure 4 shows reasons for exclusion of the first 337 excluded subjects. All of them were non-drug naive patients affected by schizophrenia. Patients entering the study must, according to their own judgment in consultation with their physician, have a condition appropriate for starting treatment with an oral antipsychotic medication or changing antipsychotic treatment. The change of the current antipsychotic medication was by far the most indicated reason for exclusion (59%).

Table 2. Recruiting centers and ITT sample (n=300).

	Center code	Patients randomized (N_O)
1.	41	26
2.	37	20
3.	28	21
4.	07	18
5.	49	15
6.	29	15
7.	44	17
8.	50	12
9.	34	15
10.	14	12
11.	15	11
12.	24	11
13.	31	12
14.	32	12
15.	11	11
16.	58	11
17.	09	7
18.	01	6
19.	46	6
20.	10	5
21.	12	4
22.	23	4
23.	38	4
24.	39	4
25.	05	3
26.	08	3
27.	20	3
28.	22	3
29.	13	2
30.	19	2
31.	02	1
32.	25	1
33.	33	1
34.	35	1
35.	57	1
		Total 300

Figure 2. Recruitment trend (updated June 2011: 301 patients randomized).

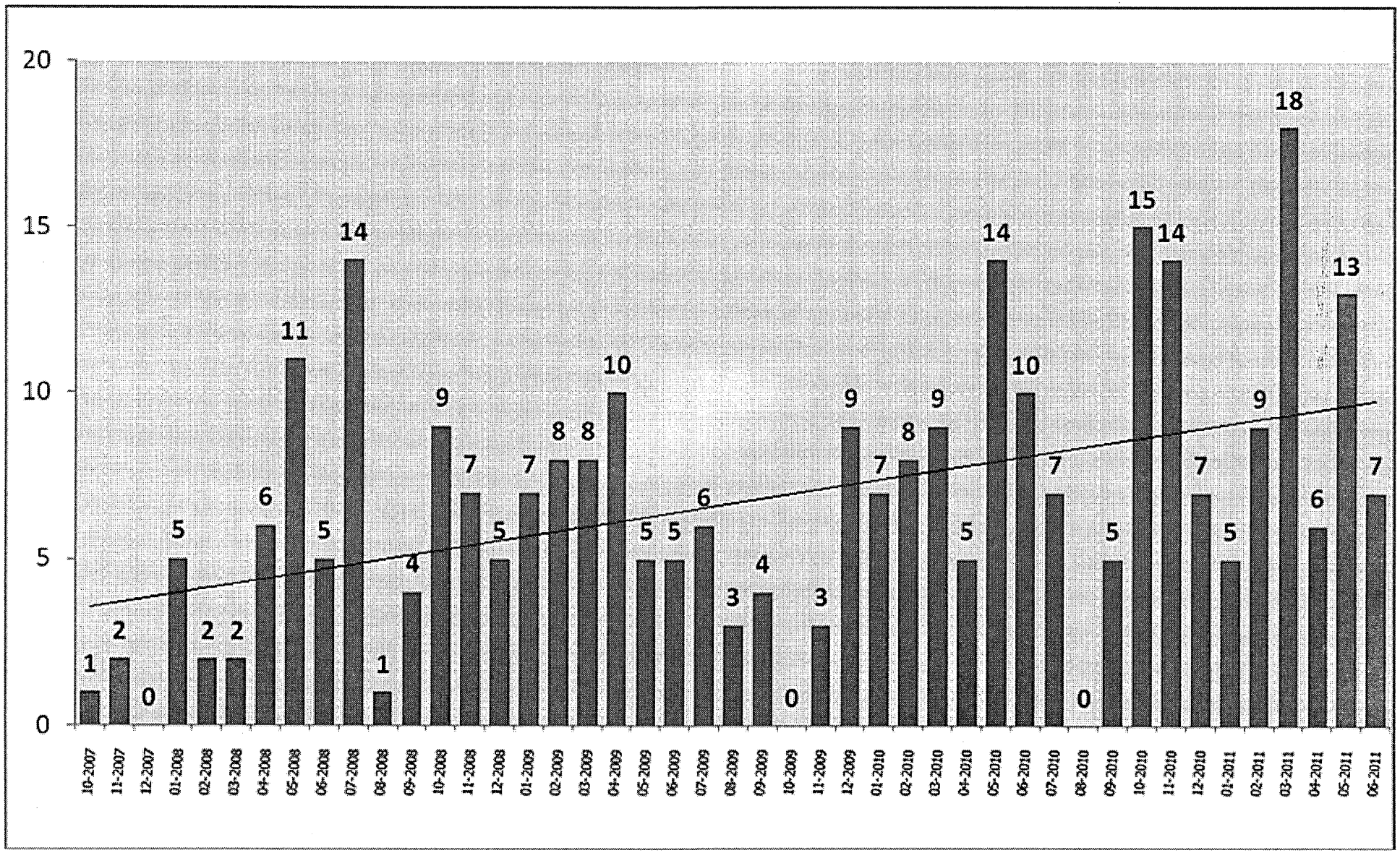


Table 3. Recruitment and screening procedure in the eight actively recruiting study sites at June 2008.

Recruiting center		Patients screened - N_o	Patients excluded - N_o	Patients recruited - N_o (%)
1. 01-07	(Genova Trust)	100	92	8 (8.0)
2. 08-10	(Como Trust)	78	72	6 (7.7)
3. 11	(Aosta Trust)	17	11	6 (35.3)
4. 12-13	(Milano-Niguarda Trust)	23	18	5 (21.7)
5. 14	(Piacenza Trust)	133	130	3 (2.3)
6. 15	(Milano-Policlinico Trust)	18	14	4 (22.2)
7. 19	(Savona Trust)	1	0	1 (100.0)
8. 22	(Milano-Rho Trust)	1	0	1 (100.0)
	Total	**371**	**337**	**34**

Figure 3. Consort Flow-chart at June 2008 (n=371).

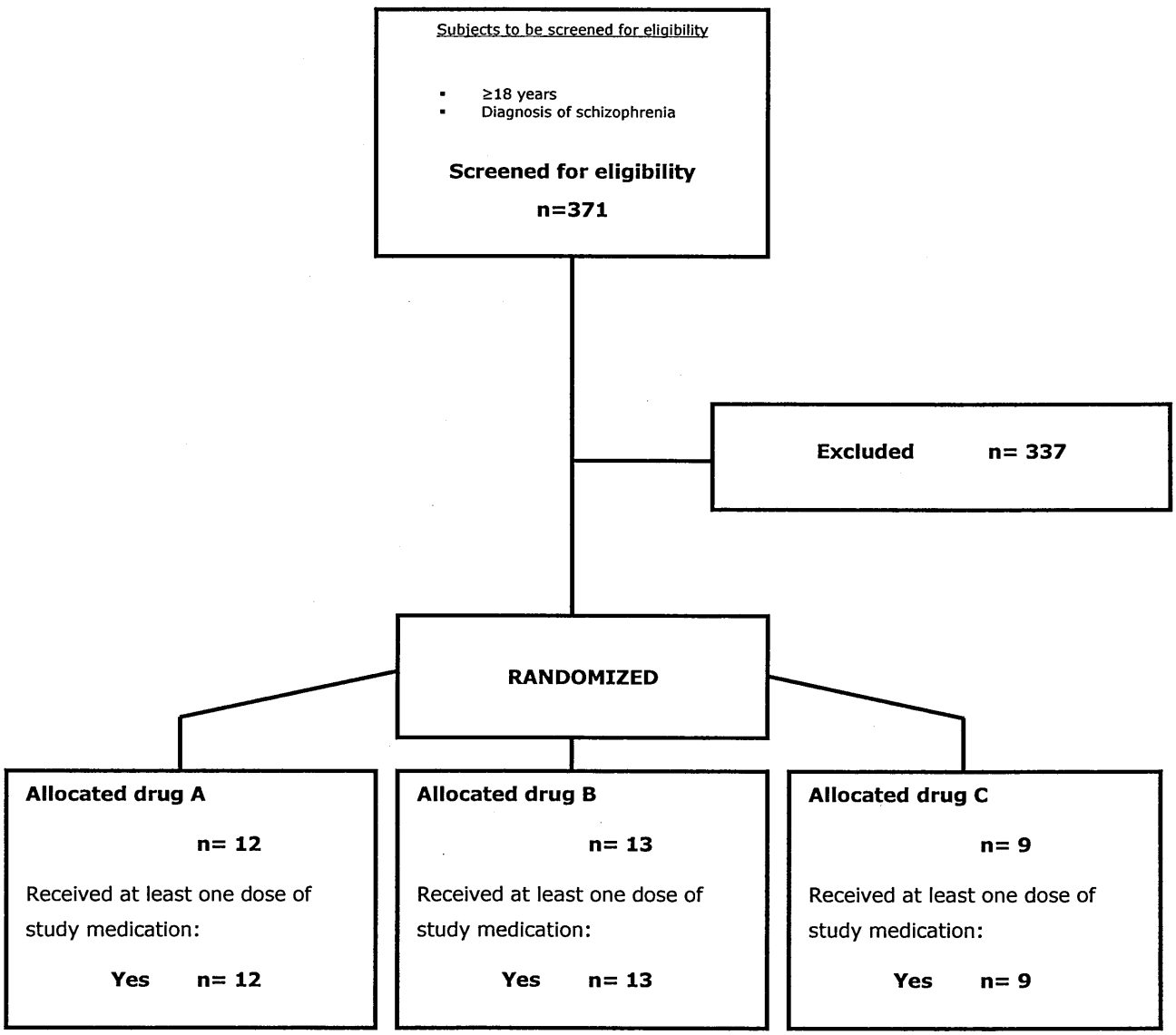
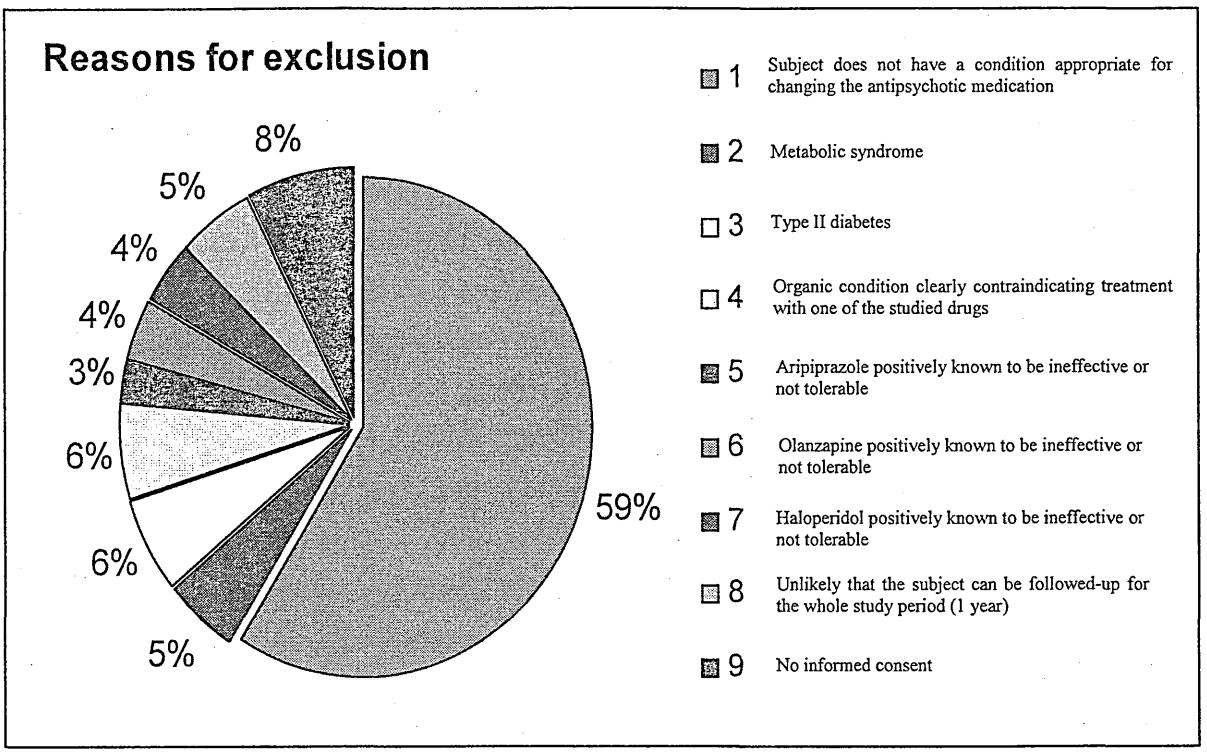


Figure 4. Reasons for exclusion at June 2008 (n=337)



From June 2008 on we took a series of countermeasures to prevent failure to meet the recruitment target.

- We intensified efforts to recruit new study centres and to accelerate approval process. In June 2008, in fact, the study had been approved by the ethics committee of only 18 centres.

- We applied for the registration of the trial in the regional registry of education initiatives. In Italy, in fact, a number of professional profiles in the health sector must, by law, acquire an assigned number of formation credits in ECM (Continuous Education in Medicine) each year. Doctors of medicine, for instance, need to acquire at least 50 credits per year. Participation to a clinical independent research "aimed at improving clinical practice in health care" (Italian Ministerial Act 17 December 2004) is considered equivalent to a full-time course or training program. The credits assigned to each specific course or educational activity are defined by the Italian Ministry of Health depending on their content and duration. On the basis of the education program we outlined, 20 credits were assigned for the GiSAS study participation. Thus, we were able to deliver 20 credits per years to compliant clinicians, nurses and clinical psychologists for all the study duration (at least three years).

- We assigned 16 annual cash awards (bursaries) to trainees attending the best performing centres using funds originally assigned to the reimbursement of the participating centres (400 Euro per patient with complete follow-up).

- We udertook a survey investigating clinicians' opinions on perceived inclusion barriers, GiSAS trial involvement and antipsychotic preference (see below: GiSAS Survey). The survey allowed us to get information on how to improve trial's participation. Consequently, we developed strategies to prompt clinicians to

continuously monitor patients' eligibility, and we intensified efforts to involve other clinicians in the recruitment process.

- We accomplished the following activities:

- presentations to inpatients and outpatients clinical teams;
- seminar and research meetings;
- face to face meetings with consultants, psychiatrists and psychologists and nurses;
- regular phone contacts;
- flyer campaigns and poster editing.

In years 2008, 2009 and 2010 we gave more than 40 oral presentations to inpatients and outpatients clinical teams outlining the study background and rationale, the aims and hypotheses and the main features of the design. We held four annual investigators conferences to summarize the study progress, to prompt clinicians to adhere to the best possible standards of trial execution and to foster discussion on difficulties and barriers to trial's participation and to patients' inclusion and follow-up.

Education activities focused on two critical issues: the existence of equipoise or uncertainty around the choice of antipsychotic drugs and the reasons underlying treatment discontinuation or switch.

As shown in Figure 2, the study recruitment lasted 45 months, from October 2007 to June 2011, and the overall monthly recruitment rate was 6.7.

Successful implementation of the remedial actions described above resulted in a significant improvement of the recruitment rate. The monthly recruitment rate in the first nine-month recruitment period, from October 2007 to June 2008, was 3.8 and became 7.0, 5.0, 7.2, and 10.4 respectively in the following four nine-month periods, from July 2008 to June 2011. Nevertheless, at the end of 2009 we had recruited only 133 patients and we were far away from the originally hypothesized sample of 800

patients. As a consequence, in January 2010, we decided to downsize the sample to about one-third of the original size (see above: paragraph *3.14.1*).

All analyses will be by full intention-to-treat (ITT) including all randomized participants who received at least one prescription of investigational drugs. Post-randomization exclusion is a critical issue related to the open nature of treatment allocation. Since we included only subjects who have taken at least one dose of study medication, some physicians and their patients could easily opt out of the trial if their allocated treatment turned not out to be the one they hoped for. To avoid this, adherence to the best possible standards of trial execution was constantly supported by trial management. In order to prevent late changes of mind we have actively prompted clinicians to prescribe the allocated drug as soon as patients were randomized. Among 301 randomizations, only one (0.3%) was not taken into account and, thus, it is not reported in Table 2. It was the first randomization (code num. 02901) of centre n° 29 and was erroneously registered before asking the patient and the treating clinician about the trial participation. Presumably this happened due to the lack of experience of a local investigator. During our periodic check of the registered calls we identified the first registered randomization of center n° 29 and, as we had not received any confirmation about the patient inclusion, we contacted the principal investigator. We found out that a local investigator, who was not the treating clinician nor the principal investigator, called the randomization number and entered the patient's data without informing the patient about the trial and without verifying if he/she were actually a possible candidate. That local investigator did so apparently unaware of the fact that the randomization could not be cancelled nor ignored. We did not exactly understand why the investigator did so. Probably he/she simply entered the patient's data to test the randomization mechanism.

At that point, we prompted the principal investigator to find out whether there were the conditions to include the patient. However, the conditions for being included were not met and both the patient and the treating clinician refused to take part to the study (i.e. no need to change medication and unwilling to participate). The drug allocated by randomization was obviously never disclosed. We believe that, in this particular case, the ITT principle should not be applied as the randomization was an error and there was no intention to include the subject in the study.

Out of the full ITT sample of 300 subjects, four patients (1.3%) were not prescribed the assigned antipsychotic and are therefore excluded from the modified-ITT population. Three of them withdrew the consent before the baseline visit; the name of the allocated drug was not disclosed and they did not change medication. These three patients were in stable conditions and there was no doubt about their capability to give or withdraw informed consent. For two of them randomization was not performed by the treating clinician. After having accurately looked into these withdrawals we concluded that there must have been some misunderstanding about trial participation.

The last case (cod num. 00904) was a more tricky one. In fact, it was the only attempt to decipher randomization concealment discovered during the trial's recruitment. The investigator did the randomization in order to find out the assignment. To fill the recruitment schedule he/she used the data of a patient who had not yet given informed consent. Thankfully, the trick was discovered and the investigator received an official reprimand.

Also in this last case, the patient did not give informed consent. However, differently from case 02901 we opted to include him in the full ITT analysis. This decision is due to the fact that this patient was actually randomized, even if with a fraudulent intent. Moreover, the investigator, who was the treating clinician, confirmed that patient

00904 was eligible. Case 02901, on the contrary, was randomized only by error and was not included because he/she was not eligible and not willing to participate. Finally, 296 patients were randomized and included over 45 months and constitute therefore the modified-ITT sample.

Collected data will be analyzed using a last-observation-carried-forward approach. Patients with no follow-up data available will be allocated to the outcome category of treatment failure. At the end of recruitment (June 2011), 166 (56.1%) of the 300 included subjects had completed the one year follow-up, 15 (5.1%) were lost to follow-up and 115 (38.8%) were still in active follow-up. All available baseline and follow-up data of the first 140 included patients had already been checked for accuracy and entered in the study database. Last twenty study subjects will be followed-up between May and June 2012. Study data are entered as soon as they are collected, so the first results will be available by end-2012.

6. GiSAS Survey

Introduction

Patient recruitment is the universal rate-limiting factor for randomized controlled trials in all medical specialties, with most trials failing to recruit their original target by their deadline [113]. Barriers to participation in RCTs are the focus of three systematic reviews which looked at issues like time constraints, scarcity of resources, the importance of the research question, patients' preference for a particular treatment, worry about uncertainty of trials, and concerns about informed consent [114-116]. No clear conclusions could be drawn because of the poor quality of the studies included. The authors therefore called for more evidence on clinicians' commitment to participation in trials. Ross and colleagues suggested that studies exploring barriers to participation should be nested within ongoing trials [114].

Pharmaceutical companies spend around 23-30% of the actual cost of a drug on its promotion, basically directed to prescribing physicians [117], and doctors update their knowledge through information that is often produced and spread by companies themselves [118]. The need to guard against undue industry influence on preferences for antipsychotics was recently highlighted by the authors of a survey conducted among 431 U.S. psychiatrists [119]. Most of them believed in the superiority of SGAs and this optimism was related to pharmaceutical representatives' contacts and to familiarity with practice guidelines.

Both the concepts of clinical equipoise and uncertainty hold that randomization is appropriate when the clinician has substantial indecision as to which treatment is likely to provide greatest clinical benefit. In order to achieve commitment to RCTs from investigators and participants the uncertainty principle should be applied in trials' recruitment [53, 120]. This will, in fact, recognize and reinforce the value of clinical

judgment and patients' autonomy and preferences and will protect the trial's internal validity regardless of whether clinicians' and patients' beliefs are correct or wrong [121]. However, the adoption of the uncertainty principle as a criterion for inclusion could introduce an excessive degree of discretion in the recruitment process thus hindering trial participation.

The inability of a human being to be objective is the ultimate source of this bias. Thus, in experimental science a variety of biases related to the awareness of treatment allocation have been described [122]. Open-label drug trials are subject to experimenter's bias which can occur in any stage of research: in specifying and selecting the study sample, in prescribing the study drugs, in measuring exposures and outcomes [123].

Davies et al. (2007) observed that only 20–37% of possibly eligible patients (those with a diagnosis of schizophrenia whose drug treatment was being changed owing to poor response or intolerance) were randomised into the CUtLASS trial and that the remaining patients were either not referred or refused to participate [26]. As there was insufficient information to determine whether the patients who participated in the trial were representative of eligible patients, this relevant selection could reduce the generalisability of the trial's results to the population of interest [26]. As part of the CutLass trial, Lloyd et al. (2005) surveyed the clinicians' attitudes regarding the relative benefits and risks of conventional and atypical antipsychotic medication and found that 90% of respondents believed that second-generation antipsychotics were associated with less severe side-effects than the conventional drugs and 38% believed that the former were superior in terms of clinical efficacy [122]. These results supported a lack of clinical equipoise in the CUtLASS trial investigators and led Davies et al. (2007) to hypothesize that the main reason for the low participation rate could be the belief in

the superiority of second-generation antipsychotics. This explanation could reassure about the selection bias and the generalizability of the study results [26].

In the EUFEST trial, to control for biases that could have occurred in prescribing the study drugs and in measuring exposures, providers' expectation for outcome was assessed [27]. In contrast with the findings by Lloyd et al. (2005), the answers obtained by 32 (64%) of the 50 site coordinators did not support a lack of clinical equipoise [122]. Haloperidol, in fact, was expected to have the worst outcome by 11 (34%) site coordinators, whereas 21 (66%) of them thought that there would be no difference between haloperidol and the SGAs [27]. To find whether expectations of psychiatrists could have led to haloperidol being discontinued more often, discontinuation rates for haloperidol were compared between patients from the sites at which haloperidol was expected to do worse and patients from the other sites. The analysis showed non-significant differences and the effect of expectations on outcome could not be proven [27].

Aim of the Survey

The uncertainty principle, which is one of the cornerstones of the credibility of clinical trials, was adopted as the leading criterion for GiSAS recruitment. Patients are assessed for eligibility only if they may benefit from changing their current antipsychotic treatment and if there is no clear indication or contraindication for any one of the three study drugs. The trial was planned to recruit 800 patients affected by schizophrenia. However, as is common in trials, patients' inclusion was a problem, and at the end of June 2008, after nine months of recruitment, only 34 patients had been randomized.

The present survey was conducted among a group of clinicians involved in the GiSAS trial. The aim was to explore clinicians' views: (a) on the feasibility and utility of clinical trials in schizophrenia; (b) on RCT inclusion barriers; (c) on the degree of uncertainty

underlying antipsychotic prescription, and (d) on the most important sources of information on antipsychotic effectiveness and tolerability.

Methods

As an ancillary study to the GiSAS trial, the present survey was addressed to all recruiting centers. These comprised 49 public facilities: 42 community mental health services, five university hospitals and two inpatient acute facilities.

An ad hoc anonymous questionnaire (see Appendix 6) was developed and posted to all clinicians working in these centers regardless of whether or not they were directly involved in the GiSAS trial. At each center, the collaboration of the trial principal investigator was obtained in order to prompt colleagues to complete and return the questionnaires. The questionnaire comprised 15 multiple-choice questions and consisted of two parts. The first collected clinicians' basic demographic and professional data (i.e. sex, age, years of clinical activity in psychiatry, main setting of clinical activity, use of official guidelines on schizophrenia, research experience). The second part was an opinion questionnaire about perceived inclusion barriers and objectives of clinical trials in schizophrenia, GiSAS trial involvement, opinions on efficacy and tolerability of antipsychotics, main factors influencing antipsychotic prescription, and sources of knowledge on antipsychotic use.

Perceived inclusion barriers were identified from the literature [114-116, 121]. The pertinence of these barriers was checked taking account of the concerns raised by the investigators during the trial recruitment. To detect critical issues in recruitment, we reviewed all trial monitoring reports and interviewed the study coordination team. We made a list of statements reflecting GiSAS investigators' attitudes and potential inclusion barriers, and we selected 11 items. After items generation we adopted the classification of Fayter and colleagues to form three critical areas: "clinical barriers",

including four items (i.e. difficulties in obtaining informed consent, poor cooperation, fear of recurrence, fear of losing therapeutic alliance); "personal barriers", including four items (ill-disposed colleagues, ethical doubts about randomization, fear of legal consequences, time constraints); "trial related barriers", including three items (inclusion/exclusion criteria; forced change of current medication; limitations to clinical choice) [115]. For the purposes of the present analysis, respondents were then classified according to the critical area they rated as the most critical.

The perceived usefulness of pharmacological RCTs in schizophrenia was investigated by asking the clinician to express 1) a positive attitude (i.e. a way of improving scientific knowledge or clinical practice) or 2) a negative attitude (i.e. a way of promoting new drugs regardless of the results). Opinions on antipsychotics included questions on the efficacy and tolerability of first-generation antipsychotics (FGAs) compared with second-generation antipsychotics (SGAs). Factors influencing antipsychotic prescription were explored by asking clinicians if they counted most on the efficacy or on the tolerability of these drugs. Finally, we explored clinicians' sources of knowledge about antipsychotics trying to understand the influence of scientific evidence, personal experience or industry-sponsored information.

Descriptive statistics for clinicians' characteristics were examined for each group. Multinomial logistic regression was used to examine the effect of psychiatrists' factors on perceived inclusion barriers, opinion about antipsychotics and GiSAS trial involvement after controlling for age, sex and work setting. Results are presented as adjusted odds ratios (OR) with associated 95% confidence intervals (CI) using "uncertain" as the reference category for antipsychotic opinion and "personal" as the reference category for inclusion barriers.

Results

The survey was conducted between June and December 2008. A total of 465 clinicians (51 residents and 414 consultants) were involved. Of them, 278 (59.8%) returned the questionnaire (See Figure 5). Table 4 shows their main personal and professional information. Nearly half (47.5%) worked in hospital, 52.5% in community mental health centers. In line with Italian residency programs psychiatrists in training worked almost only in general hospital psychiatric units (93.8%). The majority of the respondents (89.9%) had a global positive attitude towards RCTs. Only half the sample reported using clinical practice guidelines. Personal experience was the main source of knowledge on antipsychotics for half the respondents, and efficacy the main factor influencing drug choices (79.5%). Comparisons of residents and consultants showed some significant differences. Consultants were older, worked more frequently in community settings, had more often taken part in at least one RCT, and relied less on tolerability for antipsychotic choice ($p<0.01$).

The same proportions of respondents (44.6%) indicated clinical and trial-related barriers as the most important, and personal barriers were reported much less (10.8%). Comparisons of respondents classified under the most problematic inclusion barrier showed two significant differences: clinicians working in general hospital psychiatric units appeared more worried about trial (OR 3.6, CI 1.4-9.6) and clinical (OR 3.0, CI 1.2-8.2) -related barriers than personal ones ($p=0.02$). Clinicians relying more on efficacy for prescription choices report a slight but still significant difference in barrier perception, with more reporting of trial (OR 3.1, CI 1.3-7.8) and clinical (OR 3.1, CI 1.2-7.6) -related barriers than personal ones ($p=0.04$).

Comparisons of GiSAS investigators and those not involved in the trial showed three significant differences. As expected, GiSAS investigators were more likely to have had at least one previous experience in a RCT (48.5% vs. 32.4%, $p=0.05$), a positive

attitude toward RCTs (95.6% vs. 84.5%, p=0.00) and used scientific publications as the main source of knowledge on antipsychotics (52.9% vs. 40.8%, p=0.02).

Table 5 reports respondents' rating on all the 11 barriers, regardless of the aforementioned classification. The barriers more often rated as the most relevant were in the clinical area "difficulties in obtaining informed consent" (18.0%) and "fear of recurrence" (10%), in the trial related area "limitation to clinical choices" (19%) and "inclusion/exclusion criteria" (13%), in the personal area "time constraints" (5%). On the other hand, "forced change of current medication" was indicated as one of the three most relevant inclusion barriers by 128 (46%) clinicians, "limitation to clinical choices" by 111 (39.9%) clinicians, and "inclusion/exclusion criteria" by 98 (35.3%) clinicians.

Clozapine was rated as the best antipsychotic drug by 75 clinicians (27.0%), followed by olanzapine (25.5%), haloperidol (19.4%) and risperidone (16.9%). Uncertainty on the efficacy and tolerability of antipsychotics was expressed by 85 clinicians (30.6%). The majority (62.9%) trusted in the superiority of SGAs, and only 18 (6.5%) favoured FGAs. These opinions on antipsychotics appeared to be unrelated to any other factor considered in the survey.

Among the sources of information on antipsychotic drugs, we investigated the role of information received from pharmaceutical companies: 111 subjects (39.9%) indicated industry representatives among their first three sources of information in order of importance, and 103 (37.0%) indicated this source as the main one. Clinicians in the first group were slightly older than the rest of the sample (47.0 vs. 44.1 yrs; p=0.01) and more frequently used clinical guidelines (OR 1.8, CI 1.1–3.0; p=0.02). Clinicians in the second group preferred SGAs to clozapine (OR 2.1, CI 1.1–3.9; p=0.01).

In question number 10, clinicians were asked to rate the three study drugs in order of better efficacy and tolerability. The results are reported in Table 6, the majority of the

respondents rated the three drugs differently in terms of efficacy (n=215; 77%) and tolerability (n=223; 80%). For ten respondents (4%) all drugs were equally effective and for only two (1%) all drugs were equally tolerable. Haloperidol was rated as the best effective antipsychotic by most of the responders (n=153; 71%), followed by olanzapine (n=55; 26%) and aripiprazole (n=7; 3%). On the other hand, most of the responders (n=144; 65%) rated aripiprazole as the best tolerable antipsychotic, followed by olanzapine (n=67; 30%) and haloperidol (n=12; 5%). For 27 of the 40 clinicians who identified some similarities between the study drugs in terms of efficacy haloperidol and olanzapine were equally best effective. For 13 of the 37 clinicians who identified some similarities between the study drugs in terms of tolerability aripiprazole and olanzapine were equally best tolerable.

Discussion

This survey explored four critical areas: trial participation, recruitment barriers, antipsychotic preferences and sources of information on antipsychotic drug prescription. The results suggest that active involvement in the GiSAS trial was associated with a positive attitude towards RCTs and scientific evidence, and that clinical difficulties and trial-related barriers acted as important obstacles to randomization of patients, while personal barriers had less weight.

Recruitment barriers were largely related to the work setting. Clinicians working in community mental health services appeared to be more worried about personal barriers. The different clinical roles of the psychiatrists working in community teams could have influenced their perspective.

Drug choice appeared to be mostly influenced by respondents' beliefs about the efficacy of antipsychotics. Psychiatrists in training, however, seemed to give more attention to tolerability. The majority of respondents believed in the superiority of

SGAs, one-third indicating drug company representatives as the most important source of information on antipsychotics; this was associated with familiarity with clinical guidelines for schizophrenia and further optimism towards SGAs. Our findings are therefore consistent with previous research, particularly the findings reported by Arbuckle et al. (2008) [119].

With regard to antipsychotic drug preference, we must specify that in the two questions investigating opinions on drug efficacy and tolerability clozapine was not considered. In a further question, respondents were asked to rate the best antipsychotic, without limitations, and a quarter of them indicated clozapine. Efficacy was indicated as the most important criterion for prescription and this may partly explain the choice of clozapine. However, those who considered industry representatives as the main source of information preferred all the other SGAs to clozapine. Thus, the influence of industry information on respondents' optimism about SGAs was evident.

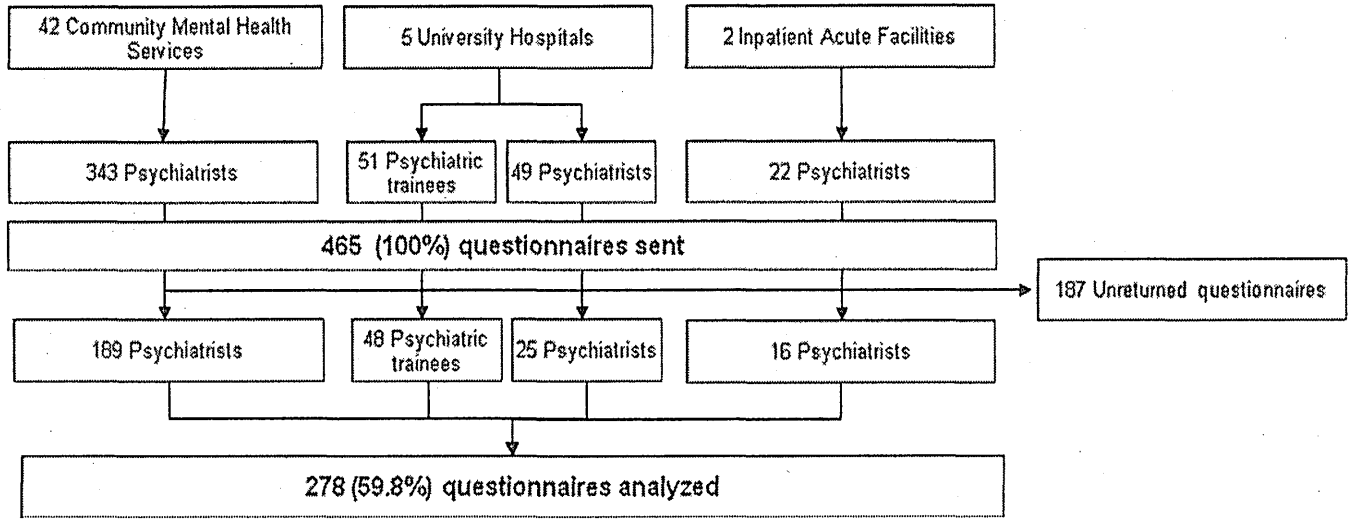


Figure 5. Gisas survey flow chart.

		Professional figures			Inclusion barriers				GiSAS trial involvement			Opinion on antipsychotics			
		Residents	Consultants	p	Clinical[a]	Personal[b]	Trial related[c]	p	No	Yes	p	Uncertain[d]	Favor FGA[e]	Favor SGA[f]	p
Sex, no. (%)															
Male	145 (52.2)	18 (37.5)	127 (55.2)		58 (48.3)	17 (58.6)	62 (51.7)		72 (50.7)	73 (53.7)		40 (47.1)	10 (55.6)	95 (54.3)	
Female	133 (47.8)	30 (62.5)	103 (44.8)		62 (51.7)	12 (41.4)	58 (48.3)		70 (49.3)	63 (46.3)		45 (52.9)	8 (44.4)	80 (45.7)	
Total	278 (100.0)	48 (100.0)	230 (100.0)	0.36	120 (100.0)	29 (100.0)	120 (100.0)	0.34	142 (100.0)	136 (100.0)	0.41	85 (100.0)	18 (100.0)	175 (100.0)	0.48
Age, mean (SD)	45.3 (9.6)	31.8 (5.4)	48.1 (7.8)	**0.00**	46.0 (9.7)	45.1 (10.3)	44.4 (9.5)	0.24	46.0 (9.9)	44.0 (9.2)	0.12	45.0 (9.9)	45.0 (9.1)	45.0 (9.6)	0.86
Years of clinical activity, mean (SD)	16.8 (9.8)	2.2 (1.2)	19.9 (7.8)	-	17.7 (9.8)	16.6 (9.9)	15.7 (9.7)	0.64	18.0 (10.2)	16.0 (9.3)	0.27	17 (10.3)	17 (10.3)	17 (9.5)	0.88
Work setting, no. (%)															
Inpatient	132 (47.5)	45 (93.8)	87 (37.8)		57 (47.5)	8 (27.6)	65 (54.2)		61 (43.0)	71 (52.2)		45 (52.9)	11 (61.1)	76 (43.4)	
Outpatient	146 (52.5)	3 (6.2)	143 (62.2)		63 (52.5)	21 (72.4)	55 (45.8)		81 (57.0)	65 (47.8)		40 (47.1)	7 (38.9)	99 (56.6)	
Total	278 (100.0)	48 (100.0)	230 (100.0)	**0.00**	120 (100.0)	29 (100.0)	120 (100.0)	**0.02**	142 (100.0)	136 (100.0)	0.34	85 (100.0)	18 (100.0)	175 (100.0)	0.15
Use of clinical guidelines, no. (%)															
Yes	141 (50.7)	26 (54.2)	115 (50.0)		57 (47.5)	19 (65.5)	57 (47.5)		72 (50.7)	65 (47.8)		43 (50.6)	8 (44.4)	86 (49.3)	
No	137 (49.3)	22 (45.8)	115 (50.0)		63 (52.5)	10 (34.5)	63 (52.5)		70 (49.3)	71 (52.2)		42 (49.4)	10 (55.6)	89 (50.9)	
Total	278 (100.0)	48 (100.0)	230 (100.0)	0.80	120 (100.0)	29 (100.0)	120 (100.0)	0.50	142 (100.0)	136 (100.0)	0.93	85 (100.0)	18 (100.0)	175 (100.0)	0.74
Experience in RCT, no. (%)															
Yes	112 (40.3)	8 (16.7)	104 (45.2)		70 (58.3)	14 (48.3)	76 (63.3)		46 (32.4)	66 (48.5)		33 (38.8)	7 (38.9)	72 (41.1)	
No	166 (59.7)	40 (83.3)	126 (54.8)		50 (41.7)	15 (51.7)	44 (36.7)		96 (67.6)	70 (51.5)		52 (61.2)	11 (61.1)	103 (58.9)	
Total	278 (100.0)	48 (100.0)	230 (100.0)	**0.00**	120 (100.0)	29 (100.0)	120 (100.0)	0.33	142 (100.0)	136 (100.0)	**0.05**	85 (100.0)	18 (100.0)	175 (100.0)	0.94
Attitude toward RCT, no. (%)															
Positive	250 (89.9)	44 (91.7)	206 (89.6)		109 (90.8)	25 (86.2)	108 (90.0)		120 (84.5)	130 (95.6)		76 (89.4)	17 (94.4)	157 (91.8)	
Negative	22 (7.9)	4 (8.3)	18 (7.8)		9 (7.5)	4 (13.8)	9 (7.5)		19 (13.4)	3 (2.2)		8 (9.4)	1 (5.6)	13 (7.6)	
Missing	6 (2.2)	0 (0.0)	6 (2.6)		2 (1.7)	0 (0.0)	3 (2.5)		3 (2.1)	3 (2.2)		1 (1.2)	0 (0.0)	5 (0.6)	
Total	278 (100.0)	48 (100.0)	230 (100.0)	0.16	120 (100.0)	29 (100.0)	120 (100.0)	0.41	142 (100.0)	136 (100.0)	**0.00**	85 (100.0)	18 (100.0)	175 (100.0)	0.79
Main source of knowledge, no. (%)															
Scientific information	129 (46.4)	18 (37.5)	111 (48.3)		60 (50.0)	16 (55.2)	50 (41.7)		58 (40.8)	72 (52.9)		38 (44.7)	7 (38.9)	85 (48.6)	
Personal experience	145 (52.2)	30 (62.5)	115 (50.0)		60 (50.0)	13 (44.8)	68 (56.7)		84 (59.2)	61 (44.9)		47 (55.3)	11 (61.1)	87 (49.7)	
Missing	4 (1.4)	0 (0.0)	4 (1.7)		0 (0.0)	0 (0.0)	2 (1.7)		0 (0.0)	3 (2.2)		0 (0.0)	0 (0.0)	3 (1.7)	
Total	278 (100.0)	48 (100.0)	230 (100.0)	0.34	120 (100.0)	29 (100.0)	120 (100.0)	0.39	142 (100.0)	136 (100.0)	**0.02**	85 (100.0)	18 (100.0)	175 (100.0)	0.71
Antipsychotic choice, no. (%)															
Efficacy	221 (79.5)	33 (68.8)	188 (81.7)		100 (83.3)	18 (62.1)	97 (80.8)		112 (78.9)	109 (80.1)		68 (80.8)	16 (88.9)	137 (78.3)	
Tolerability	52 (18.7)	15 (31.2)	37 (16.1)		20 (16.7)	11 (37.9)	19 (15.8)		28 (19.7)	24 (17.6)		16 (18.8)	2 (11.1)	34 (19.4)	
Missing	5 (1.8)	0 (0.0)	5 (2.2)		0 (0.0)	0 (0.0)	4 (3.4)		2 (1.4)	3 (2.2)		1 (1.2)	0 (0.0)	4 (2.3)	
Total	278 (100.0)	48 (100.0)	230 (100.0)	**0.00**	120 (100.0)	29 (100.0)	120 (100.0)	**0.04**	142 (100.0)	136 (100.0)	0.70	85 (100.0)	18 (100.0)	175 (100.0)	0.66

[a]**Clinical barriers:** difficulty obtaining patient's informed consent; poor patient's cooperation; fear of recurrence; fear of losing therapeutic alliance; [b]**Personal barriers:** colleagues are not well disposed; ethic doubts on randomization; fear of legal consequences; time constrain

[c]**Trial related barriers:** inclusion/exclusion criteria; forced change of current medication; study protocol limits clinical choices; [d]**Uncertain:** no difference for both tolerability and efficacy + FGAs better for efficacy and SGAs better for tolerability + SGAs better for efficacy and FGAs better for tolerability

[e]**Favor FGA:** FGAs better for both efficacy and tolerability + FGAs better for efficacy and no difference in tolerability + FGAs better for tolerability and No difference in efficacy; [f]**Favor SGA:** SGAs better for both efficacy and tolerability + SGAs better for efficacy and no difference in tolerability + SGAs better for tolerability and No difference in efficacy

p < 0.05; p < 0.01

Table 4. Socio-demographic and professional characteristics, main source of knowledge on antipsychotics and main factors influencing prescriptions for 278 clinicians by type of main inclusion barrier in schizophrenia RCTs, GiSAS trial involvement and opinion on first-generation (FGAs) and second-generation (SGAs) antipsychotics.

Table 5. Inclusion barriers indicated as the most relevant by the 278 respondents.

	Inclusion barriers	no.	%
1.	Study protocol limits clinical choices	53	19.1
2.	Difficulties in obtaining patient's informed consent	50	18.0
3.	Inclusion/exclusion criteria	35	12.6
4.	Forced change of current medication	32	11.5
5.	Fear of recurrence	29	10.4
6.	Poor patient's cooperation	28	10.2
7.	Time constraints	13	4.7
8.	Fear of losing therapeutic alliance	13	4.7
9.	Colleagues are not well disposed	10	3.6
10.	Ethic doubts about randomization	6	2.2
11.	Fear of legal consequences	0	0.0
	Missing	9	3.2
	Total	278	100.0

Table 6. Opinions on relative efficacy and tolerability of haloperidol, olanzapine and aripiprazole among responders who rated the three drugs differently (n=215 for efficacy; n=223 for tolerability).

Rank order	Haloperidol	Olanzapine	Aripiprazole
Efficacy* , no. (%)			
1	153 (71.2%)	55 (25.6%)	7 (3.3%)
2	53 (24.7%)	143 (66.5%)	19 (8.8%)
3	9 (4.0%)	17 (7.9%)	189 (87.9%)
Total	215 (100.0%)	215 (100.0%)	215 (100.0%)
Tolerability** , no. (%)			
1	12 (5.4%)	67 (30.0%)	144 (64.6%)
2	38 (17.0%)	134 (60.1%)	51 (22.9%)
3	173 (77.6%)	22 (9.9%)	28 (12.6%)
Total	223 (100.0%)	223 (100.0%)	223 (100.0%)

* 1= best effective drug; 3= least effective drug
**1= best tolerated drug; 3= least tolerated drug

As for the three study drugs, it seemed that most of the respondents had clear ideas about their relative efficacy and tolerability. Haloperidol was rated as the best antipsychotic in terms of efficacy and the worst in terms of tolerability. Aripiprazole, on the other hand, was rated as the best antipsychotic in terms of tolerability and the worst in terms of efficacy. The middle-ranking position of olanzapine was perhaps the best result. Only a scant minority of respondents, in fact, rated this drug as the worst in terms of efficacy or tolerability. Although not completely consistent with best available evidence, these results are not surprising or unreasonable. At the time the present survey was performed (2007) aripiprazole was the latest antipsychotic with a good reputation for tolerability and a still doubtful reputation for effectiveness. Haloperidol, a highly potent FGA, has been prescribed for many years in Italy and its use was frequently linked to clinically evident extrapyramidal symptoms [83-85]. Finally, olanzapine, a first-choice SGA, was the most ever prescribed antipsychotic in Italy and was positively known to cause very few extrapyramidal symptoms [81, 82].

Taking into account the threats to the validity of studies such as our that were set out by Fayter and colleagues we can highlight the strengths and limitations of the present study [115]. To our knowledge, this is the first survey of recruitment barriers nested in a large pragmatic trial on schizophrenia. However, this was both a strength and a limitation because there were no standardized instruments to rely on. As in other similar surveys the response rate was about 60%, and considering there was no reward and that it required some time we believe the response rate was acceptable [27, 119, 123]. We clearly described the survey design, data collection and analysis. To avoid selection bias, and because we believed that group attitudes can strongly influence the beliefs surveyed, we asked all the clinicians working in the trial centres to participate.

The respondents' opinions on best antipsychotic drugs partially mirrored the actual prescription patterns of Italian clinicians. Olanzapine and risperidone, in fact, were the two most prescribed antipsychotics in Italy at the time the survey was being conducted, and haloperidol was by far the most prescribed FGA [124]. The generalizability of the results, however, suffers some limitations. Although the survey was anonymous, social desirability might have affected responses. In fact, 46% of respondents indicated scientific information as their main source of knowledge on antipsychotics and this was much more than expected. Moreover, response patterns might have been influenced by the characteristics of responders since results were not adjusted for non-response. Other limitations pertain to the validity of the survey: we did not allow clinicians to make additional comments and focused only on the clinicians' perspective.

These findings pertain primarily to the routine clinical practice of Italian mental health services. The differences between community and hospital teams, for instance, are likely to be related to the specific Italian context. However, the findings on attitudes towards RCTs or on antipsychotic preference could hardly be explained as a peculiarity of our sample and are therefore generalizable to other settings or situations.

Identifying the most important recruitment barriers in a trial is crucial for attaining of the objectives.

The GiSAS investigators mainly complained about system-related barriers, and personal barriers were given less weight. The lack of uncertainty about the relative efficacy and tolerability of FGAs and SGAs, however, could have affected clinicians' attitude towards trial participation, de facto acting as a personal barrier. In turn, the influence of industry-mediated information could have had a role in affecting clinician's opinions on SGAs.

Further investigation on the relationship between the identified inclusion barriers and the actual recruitment rate could lead to a better understanding of the phenomenon.

CHAPTER III

CONSIDERATIONS ON STUDY ENPOINTS

7. Drug discontinuation as an endpoint for effectiveness

Background

Treatment discontinuation is a widely accepted broad and composite measure of treatment efficacy, safety, and tolerability. The discontinuation of medium- long-term pharmacotherapy could, in fact, be related to the lack of efficacy, the development of adverse events, and the patients' unwillingness to continue treatment, which are all negative endpoints.

Treatment discontinuation in clinical trials has been used as a measure of treatment ineffectiveness in a variety of disorders [125, 126]. Time to all-cause treatment discontinuation has been adopted as primary outcome in a number of independent pragmatic RCTs on antipsychotic drug in schizophrenia [21-27, 127].

In order to understand the relative roles of efficacy and tolerability on treatment discontinuation in schizophrenia two similar post-hoc pooled analyses of clinical trials within the Eli Lilly and Company database were performed [128, 129]. Data from four double-blind and actively controlled RCTs including 1627 patients were pooled and analysed to assess the pattern and reasons for antipsychotic discontinuation regardless of the treatment groups. In the analysis by Liu-Seifert et al. (2005) only a slight majority of patients (53%) discontinued treatment within 24-28 weeks most of them stopping the assigned medication at an early stage. Poor response or worsening was the most frequent reason for stopping medications (36%), whereas poor tolerability accounted for a minority of discontinuations. Moreover, at each timepoint completers had significantly lower PANSS total scores than non completers. Discontinuation for poor response resulted to be more often linked to patient perception than to clinicians' conclusions alone (80% vs. 20%) and discontinuation due to patients' perception of

poor response occurred early in the course of treatment [128]. The analysis by Dunayevich et al. (2007) focused on time to all-cause treatment discontinuation showing that longer treatment retention was associated with greater improvements in symptoms and in all assessed functional domains ($p<0.05$) [129]. In another post hoc pooled analysis of the same four RCTs from the Eli Lilly and Company database, Kinon et al. (2006) compared differential rates of treatment discontinuation in clinical trials as a measure of treatment effectiveness between olanzapine and other atypical antipsychotics [130]. The analysis, which included 822 olanzapine-treated and 805 risperidone-, quetiapine-, or ziprasidone-treated patients, showed that the rates of discontinuation for poor response or symptom worsening were significantly lower for olanzapine (14.23%) than for the other atypical antipsychotics (24.60%; $p<0.0001$). No statistically significant differences in terms of discontinuation rates for intolerability were found by treatment groups (olanzapine, 5.60% vs. other antipsychotics, 7.45%; $p=0.13$) [130].

Continuous pharmacological treatment at therapeutic doses is essential for the care of people affected by schizophrenia, but it is also considered an important goal for the effective management of other psychiatric disorders such as major depression or bipolar disorder [131, 132]. Some studies suggests that the duration of antidepressant treatment might be influenced by medication choice and tolerability [133-136]. Evidence derived from observational studies indicated that patients treated with tricyclic antidepressants were more likely to early discontinue their treatment compared with patients treated with newer classes of antidepressants [137-139].

Treatment persistence has been adopted as an indicator of effectiveness in a number of pharmaco-epidemiological studies on antipsychotic or antidepressant prescription [140-143]. Kreyenbuhl et al. (2010) compared time to discontinuation of FGAs and SGAs in the treatment of schizophrenia [142]. Data on antipsychotic prescription in

years 2004-2006 were drawn from the U.S. department of Veterans Affairs' pharmacy and health care utilization databases. The analysis, involving 2138 patients starting a new antipsychotic treatment, showed that the majority of the sample (84%) discontinued their index antipsychotic during the follow-up period. Only risperidone showed a lower cumulative proportion of persistent individuals if compared with olanzapine (adjusted hazard ratio=1.25, 95%; CI: 1.02-1.30, p=0.25) [142]. Vlahiotis et al. (2011) identified in the U.S. Marketscan Commercial Claims database 16659 new antidepressant prescription episodes with the aim of comparing discontinuation rates at 180 days between generic and brand SSRI or SNRI [143]. 47.8% initiated a brand-name antidepressant whereas 52.2% initiated a generic antidepressant. The study results showed no statistically significant differences in terms of adjusted odds of discontinuation between the two classes of products [143].

Further observational studies using larger samples in routine clinical practice may be useful in understanding differences in discontinuation rates across medications.

As mentioned above, the most indicated reason for the exclusion of patients from the GiSAS trial was the fact that the clinicians did not consider appropriate to change their antipsychotic medication. Therefore, education activities aimed at improving recruitment focused on two critical issues: a) the existence of equipoise/uncertainty around the choice of antipsychotic drugs and b) the reasons underlying treatment discontinuation or switch. A closer look was given to the concept of treatment discontinuation as an endpoint for effectiveness using a secondary analysis of existing data (see APPENDIX 7) and a preliminary analysis of GiSAS trial data (see Section 8).

The secondary analysis of existing data focused on antidepressants' dispensing trends in a large population sample of northern Italy (APPENDIX 7: reboxetine study). Drug-dispensing data were drawn from the regional drug administrative Lombardy database (Italy), they were managed and analyzed using an anonymous patient code, after obtaining the authorization by the Regional Health Ministry. The dataset contained all prescription records for 1 704 923 inhabitants of three administrative provinces from January 1, 2000 to December 31, 2007.

Taking the cue from a recently published meta-analysis we performed a pharmacoepidemiological study comparing the use of reboxetine, fluoxetine, paroxetine and mirtazapine in a large sample of adults in Lombardy (Italy) [144]. Although reboxetine has been prescribed for many years in Europe for the treatment of depression, Eyding et al (2010) concluded that it was ineffective and potentially harmful [144]. We aimed, therefore, at confirming those results comparing the use of reboxetine with that of other antidepressants in terms of prescription trends and rates of prolonged and persistent use. The study was not only meant to possibly corroborate recent experimental findings through naturalistic evidence. In our view, it represented a unique occasion to find out whether the prescription patterns of a drug later found ineffective by research evidence would have shown earlier its limits.

Prevalent and incident use of the study antidepressants were analysed. The proportion of prolonged to occasional use and of persistence to non-persistence among reboxetine, fluoxetine and paroxetine users were compared. A mean of 211 883 subjects per year were prescribed and dispensed one of the study drugs across the study period. In years 2000-2006 the prescriptions of fluoxetine, paroxetine and mirtazapine increased. On the contrary, the use of reboxetine progressively declined and was associated with higher discontinuation rates. In particular, the rise in the prescriptions of paroxetine and fluoxetine from 2000 to 2006 was dramatic: from 0.42% to 1.16% and from 0.18% to 0.39%, respectively. Also the prescripition rates of

mirtazapine gradually increased all through the study period: from 0.07% in 2000 to 0.13% in 2006. On the contrary, the prescription rates of reboxetine progressively decreased from 0.20% in 2000 to 0.04% in 2006. The overall proportion of prolonged to occasional use was significantly lower for reboxetine (42%) than for paroxetine (57%; OR 0.55, 95% IC 0.53-0.57, $p<0.001$) and fluoxetine (58%; OR 0.53, 95% IC 0.51-0.55, $p<0.001$). Similarly, the overall proportion of persistence to non-persistence was significantly lower for reboxetine (23%) than for paroxetine (34%; OR 1.67, 95% IC 1.56-1.79, $p<0.001$) and fluoxetine (36%; OR 1.89, 95% IC 1.76-2.03).

To summarize, reboxetine showed a progressive decrease in prescription rates in years 2000-2006 and was associated with worse treatment retention than paroxetine and fluoxetine. Our observational findings were consistent with recent experimental evidence. The higher discontinuation rates of reboxetine could have affected its perception as a poorly effective antidepressant and this could have resulted in the decline of its prescriptions.

Antipsychotic and antidepressant prescription patterns are obviously different. However, reasons for discontinuation are very similar across different classes of drugs [131, 132]. As mentioned above, we decided to focus on reboxetine because its case represented a unique occasion to test out if its lack of efficacy would have been translated into a higher proportion of treatment discontinuations. As a consequence, our results added validity to the assumption that differences in discontinuation rates reflect differences in effectiveness in actual clinical practice and were therefore used in trial related education activities.

8. Preliminary analysis of the first 114 patients enrolled in the GiSAS trial.

Baseline characteristics of the sample

As on June 2010, 120 subjects completed their one year follow-up period. In October 2010, all available baseline and follow-up data of those subjects had been checked for accuracy and entered in the study database. Six subjects (5%) were excluded from the present analysis because of inconsistencies in the data.

Table 8 shows the sociodemographic characteristics of this sample of patients affected by schizophrenia. There were around 20 percent of missing data with respect to "marital status", "years of education" and "working status". The mean age of the sample was 40 years. They were mostly males (56%) and unmarried (70%). The majority lived at home (84%) and with their parents (76%).

Table 9 shows the clinical characteristics of the sample. They were mostly outpatients with a mean duration of contact with mental health services of eight years. Most of them (72%) were on antipsychotic oral medication at study entry, 16% were on long-acting medication or both, and 12% were not taking any antipsychotic medication.

Although patients with comorbidities (with the exception of metabolic syndrome and diabetes type 2) were not excluded from the study, only 26 (23%) subjects had a medical disorder, 8 (7%) abused of alcohol or other substances, 14 (12%) were affected by medication-related problems and no one was affected by tardive dyskinesia. Overall, 82 (72%) subjects were free from any major medical comorbidity, from any medication-related problem, and from alcohol/substance abuse or dependence.

Psychiatrists were asked to rate compliance of subjects with at least one prior adequate antipsychotic trial on a four-point Likert scale on the basis of their clinical judgment. For the majority of them (63%) compliance was rated as satisfactory.

Clinicians were also asked to collect patients' opinion on the efficacy and tolerability of antipsychotic drugs through statements that utilized a four-point Likert scale. Most of respondents rated those drugs positively: 68 (63%) subjects were satisfied in terms of efficacy, 69 (64%) in terms of tolerability. Among them, 52 (48%) were totally satisfied and 29 (27%) were satisfied in terms of efficacy but dissatisfied in terms of tolerability (or viceversa). Only 16 (15%) subjects were totally dissatisfied.

The mean GAF score was 46.85 with a standard deviation of 15.67. 89 (82%) patients scored below 61 which is a widely adopted cut-off point for moderate disability, 61 of them (68%) scored below 51 (severe disability). The mean BPRS score was 56.82 with a standard deviation of 17.99. We adopted a cut-off of 38 or greater for BPRS score, as in a previous paper it showed to be a reliable indicator of illness severity [145]. In the present sample, 97 (90%) patients scored above that cut-off score. Overall, 85 (78%) patients satisfied both GAF and BPRS criteria for at least moderate severity and disability.

Table 9 shows LUNSERS side-effect scores. Psychic and extrapyramidal reactions had the higher scores: 12.10 (SD=6.08) and 4.53 (SD=4.11) respectively. Psychic reactions were the most frequently reported adverse effects (98%), followed by extrapyramidal reactions (88%), anticholinergic reactions (76%) and autonomic reactions (71%). We adopted the cut-off scores proposed by the authors of the scale and we classified patients in terms of the overall side-effect burden and in terms of the reliability of their responses (red-herring items) [102] . Most of the sample (76%) reported a low burden of antipsychotic induced side-effects (total scores 0-40), and only 24% reported a medium burden (total scores 41-80). We discriminated between reliable and unreliable subjects adopting a cut-off of 20 points on the red-herring subscale (see paragraph 3.5). Unreliable subjects (n=5) scored significantly higher in all the seven subscales of

adverse effects and in the LUNSERS total score (Mann-Whitney, $p<0.05$ for all comparisons).

Data from clinical examination and electrocardiogram are shown in Table 10: clinical signs of prolactin dysregulation were evident in 14 (12%) subjects, extrapyramidal signs were evident in 9 (8%) subjects, and ECG abnormalities were evident in 10 (9%) subjects with only 3 (3%) subjects showing a borderline or prolonged QTc.

Subjects with evidence of extrapyramidal symptoms had a higher mean extrapyramidal LUNSERS subscore (n=7; mean=9.00, SD=4.65) than those without (n=76; mean=4.31, SD=3.92; p=0.010, Mann-Whitney). Subjects with evidence of endocrine abnormalities had a higher mean endocrine LUNSERS subscore (n=10; mean=5.40, SD=4.22) than those without (n=74; mean=2.95, SD=3.13; p=0.054, Mann-Whitney).

Table 11 shows baseline levels of prolactin and of metabolic syndrome variables and baseline anthropometric indicators of obesity. Due to missing data, a complete evaluation of metabolic syndrome was not possible for 45 (39%) subjects. Missing data were found for blood analysis parameters (n=37 subjects), for hypertension (n=8), and for abdominal obesity (n=13).

Among the subjects with complete data, 41% had hypertension, 42% had abdominal obesity, 48% had high fasting triglycerides, 5% had high fasting blood glucose, 53% had low fasting HDL.

Although all subjects had been screened negative for metabolic syndrome by the study investigators, 22 (19%) resulted positive after central blood tests. Anthropometric indicators of obesity had less missing data: 15 (13%) for waist-to-hip ratio (WHR) and 13 (11%) for waist-to-height ratio (WHtR). Among the subjects with complete data, 71% had a high WHR and 49% had a high WHtR.

Comparing males and females in terms of baseline metabolic syndrome variables and anthropometric measures we found three statistically significant differences: more

males had high triglycerides (59% vs. 33%; p=0.022, Chi-Square), more females were affected by abdominal obesity (57% vs. 30%; p<0.006, Chi-Square), and males had higher mean WHR (n=56; mean=0.98, SD=0.07) than females (n=43; mean=0.91, SD=0.13; p=0.000, Mann-Whitney).

Ten-year cardiac risk estimates including behavioural and anthropometric factors

Schizophrenia has been associated to increased mortality rates compared with the general population [66]. Many well-established cardiac risk factors could contribute to an elevated incidence of cardiac events in schizophrenic patients [67]. Moreover, some evidence supports the hypothesis that long-term antipsychotic therapy may play a role in their increased cardiovascular mortality [70].

Various tools to predict adverse cardiovascular events have been developed. Most of them are based on the Framingham model and have been devised from longitudinal community-based cohort studies [146, 147]. However, the Framingham-based models do not include anthropometric indicators and lifestyle variables like waist circumference, physical activity, smoking or alcohol consumption, which could play an important role in the increased mortality of schizophrenia.

In a recent study a global cardiovascular prediction tool incorporating traditional, anthropometric, and behavioural risk factors was applied by Sacco et al. (2009) to the results of the Northern Manhattan Cohort Study (NOMAS) in order to improve primary prevention strategies [74]. Subjects were enrolled if they were at least 40 years of age, lived in a pre-defined area of Northern Manhattan, and did not have a history of stroke. A global vascular risk score (GVRS) of 9.0 implied a 10-year probability of developing cardiovascular events of 20%, a GVRS of 8.2 implied a 10-year probability of 10%, a GVRS of 6.6 implied a 10-year probability of 2%. The authors showed a significant improvement in the prediction of global vascular risk by adding behavioural

risk factors and waist circumference to the traditional cardiovascular profile. Waist circumference, for instance, which has never been included in prior models was a better predictor than body mass index in the study cohort [74]. Moreover, rather than use multiple risk factor tables, a model adaptable to Internet-based or handheld programmable devices was implemented. Simple online entry of the basic variables is available to permit calculation of GVRS [148]. The GVRS tool uses continuous variables rather than categorical classifications (fasting blood sugar instead of diabetes, blood pressure instead of hypertension), and this may provide more precise risk assessments [74].

Sociodemographic variables	
Gender	
Male	64 (56.1)
	(missing n=0)
Marital status	
Single	63 (70.0)
Married or cohabiting	20 (22.2)
Legally separated/divorced	7 (7.8)
Widowed	0 (0.0)
	(Missing n=24)
Living status	
Home	92 (84.4)
Residential facility	17 (15.6)
	(Missing n=5)
Living condition	
Alone	8 (7.4)
With family	82 (75.9)
With others	18 (16.7)
	(Missing n=6)
Years of education, mean (SD)	10.94 (2.94)
	(missing n=22)
Working status	
Competitive employment	30 (33.7)
Supported employment	7 (7.9)
Retired	2 (2.2)
Housewife	5 (5.6)
Student	2 (2.2)
Unemployed	16 (18.0)
Disability pension	27 (30.3)
	(missing n=25)
Age yrs, mean (sd)	40.27 (12.08)

Values are presented as n (%) unless otherwise indicated.

Table 8. Sociodemographic characteristics of the sample (n=114).

Clinical variables	
Years since first psychiatric contact, mean (SD)	
First-ever contact	13.64 (11.97)
First contact with the study centre	8.36 (8.89)
	(missing n=10)
Inpatient, yes	21 (18.4)
Alcohol or substance abuse, yes	8 (7.0)
Past suicide attempts, yes	17 (14.9)
Number of suicide attempts, median (min, max)	1.00 (1, 15)
	(missing n=6)
Tardive dyskinesia, yes	0 (0.0)
Other medication-related problems	14 (12.3)
Neurological disorders	3 (2.6)
Cardiovascular disorders	7 (6.1)
Other disorders	16 (14.0)
Previous antipsychotic treatments*,** (n=108)	
Compliance	
Unsatisfactory	8 (7.0)
Uncertain	26 (22.8)
Satisfactory	72 (63.2)
Not assessable	8 (7.0)
Patient evaluation on efficacy	
Absolutely negative	2 (1.9)
Partially negative	32 (29.6)
Positive enough	52 (48.1)
Absolutely positive	16 (14.8)
Not assessable	6 (10.6)
Patient evaluation on tolerability	
Absolutely negative	3 (2.8)
Partially negative	28 (25.9)
Positive enough	55 (50.9)
Absolutely positive	14 (13.0)
Not assessable	8 (7.4)
Current antipsychotic treatment	
Oral medication	82 (71.9)
Long-acting medication	9 (7.9)
Both	9 (7.9)
No medication	14 (12.3)
GAF score, mean (SD)	46.85 (15.67)
	(missing n=5)
BPRS total score, mean (SD)	56,82 (17.99)
	(missing n=6)
LUNSERS*** (n=86)	
Extrapyramidal reactions, mean (SD)	4.53 (4.11)
Indicator of Parkinsonism, mean (SD)	0.55 (0.91)
Indicator of akathisia, mean (SD)	5.18 (2.97)
Psychic reactions, mean (SD)	12.10 (6.08)
Allergic reactions, mean (SD)	1.42 (1.96)
Anticholinergic reactions, mean (SD)	2.76 (2.87)
Other autonomic reactions, mean (SD)	2.48 (2.70)
Endocrine reactions, mean (SD)	3.07 (3.28)
Others adverse reactions, mean (SD)	2.45 (2.00)
Red herring items, mean (SD)	3.23 (3.64)
Total score, mean (SD)	28.82 (17.54)

Values are presented as n (%) unless otherwise indicated. GAF=Global Assessment of Functioning; BPRS=Brief Psychiatric Rating Scale; LUNSERS=Liverpool University Neuroleptic Rating Scale.
*in the previous 2-year period; **Subject with no past adequate antipsychotics trials were excluded; ***Subjects not on antipsychotic medication at study entry were excluded.

Table 9. Clinical characteristics of the sample at baseline (n=114).

Clinical and instrumental exams		
Endocrine signs and symptoms	14	(12.3)
Galactorrea	2	(1.8)
Gynecomastia	2	(1.8)
Dysmenorrhea	6	(5.3)
Menstrual irregularities	11	(9.6)
Extrapyramidal signs and symptoms	9	(7.9)
Akathisia	5	(4.4)
Tardive dyskinesia	0	(0.0)
Parkinsonism	5	(4.4)
Dystonia	1	(0.9)
Heart rate, mean (SD)	76.55	(13.1)
ECG abnormalities	10	(8.8)
QTc, mean (SD)	394.89	(30.9)
Normal*	98	97.0)
Borderline**	1	(1.0)
Prolonged***	2	(2.0)
	(missing n=13)	

Values are presented as n (%) unless otherwise indicated.
*Normal: <430 msec (males), <450 msec (females); **Borderline: 431-450 (males), 451-470 (females); ***Prolonged: >450 (males), >470 (females)

Table 10. Data on baseline electrocardiographic and clinical examination (n=114).

	Males	Females		Total
Diastolic blood pressure[§], mean (SD)	74.45 (20.67) *(missing n=0)*	73.00 (23.14) *(missing n=0)*		73.82 (21.70) *(missing n=0)*
Systolic blood pressure[§], mean (SD)	117.19 (33.06) *(missing n=0)*	112.10 (36.83) *(missing n=0)*		114.96 (34.69) *(missing n=0)*
Antihypertensive medication[§], yes	2 (3.1)	3 (6.0)		5 (4.4)
Hypertension, yes	24 (40.0) *(missing n=4)*	19 (41.3) *(missing n=4)*		43 (40.6) *(missing n=8)*
Waist circumference[§], mean (SD)	97.30 (14.43)	92.75 (16.50)		95.32 (15.45)
Abdominal obesity, yes	17 (29.8) *(missing n=7)*	25 (56.8) *(missing n=6)*	**	42 (41.6) *(missing n=13)*
Metabolic syndrome[§], yes	0 (0.0)	0 (0.0)		0 (0.0)
Fasting TG[§§], mean (SD)	163.84 (94.53)	139.09 (83.63)		153.23 (90.29)
High TG, yes	26 (59.1) *(missing n=20)*	11 (33.3) *(missing n=17)*	*	37 (48.1) *(missing n=37)*
Fasting HDL[§§], mean (SD)	25.72 (18.86)	30.78 (24.97)		27.94 (21.80)
Low HDL, yes	23 (52.3) *(missing n=20)*	18 (54.5) *(missing n=17)*		41 (53.2) *(missing n=37)*
Fasting glucose[§§], mean (SD)	61.67 (44.10)	57.52 (43.26)		59.85 (43.60)
High glucose, yes	3 (6.8) *(missing n=20)*	1 (3.0) *(missing n=17)*		4 (5.2) *(missing n=37)*
Number of risk factors[§§],				
0	6 (9.4)	4 (8.0)		10 (8.8)
1	10 (15.6)	6 (12.0)		16 (14.0)
2	11 (17.2)	10 (20.0)		21 (18.4)
3	8 (12.5)	8 (16.0)		16 (14.0)
4	3 (4.7)	1 (2.0)		4 3.5)
5	2 (3.1)	0 (0.0)		2 (1.8)
Missing	*24 (37.5)*	*21 (42.0)*		*45 (39.5)*
Total	64 (100.0)	50 (100.0)		114 (100.0)
Metabolic syndrome[§§], yes	13 (20.3)	9 (18.0)		22 (19.3)
Prolactin[§§], mean (SD)	17.55 (16.20)	26.89 (28.07)		21.55 (22.40)
High prolactin, yes	19 (44.2) *(missing n=20)*	9 (27.3) *(missing n=17)*		28 (36.8) *(missing n=37)*
WHR, mean (SD)	0.98 (0.07)	0.91 (0.13)	**	0.95 (0.10)
High WHR, yes	41 (73.2) *(missing n=8)*	29 (67.4) *(missing n=7)*		70 (70.7) *(missing n=15)*
WHtR, mean (SD)	0.58 (0.11)	0.57 (0.11)		0.57 (0.11)
High WHtR, yes	26 (45.6) *(missing n=7)*	24 (54.5) *(missing n=6)*		50 (49.5) *(missing n=13)*

Values are presented as n (%) unless otherwise indicated. TG= triglycerides; HDL=high-density lipoproteins; WHR=waist-to-hip ratio; WHtR=waist-to-height ratio; [§]local blood analysis; [§§]central blood analysis; *p<0.05; **p<0.01.

Table 11. Gender differences in baseline levels of metabolic syndrome variables and of prolactin and in baseline anthropometric indicators of obesity (n=114; Chi-Square or Mann-Whitney test where appropriate).

As all the risk factors and indicators included in the NOMAS model were already collected for the GiSAS trial, we could apply the model to our sample. Among the first 114 recruited subjects, 74 (65%) were at least 40 years of age and were therefore eligible for the GVRS calculation. As requested by the trial inclusion criteria, none of them was diabetic or diagnosed as having metabolic syndrome. However, when the results of the centralized analyses were taken into account, 18 of them fulfilled at least three criteria of metabolic syndrome. None of them had an history of stroke (as in the NOMAS cohort) or was affected by peripheral vascular disease. For 27 subjects (36%) some variables of the model were missing. Thus, we were able to calculate GVRS for only 47 subjects (41%).

The variables of the NOMAS global vascular risk model are shown in Table 12 and the results of the GVRS calculation are reported in Table 13. Most of the subjects of our sample had a low cardiovascular risk. In particular, the majority of the sample (55%) had both a 5- and a 10-year risk below 5%. Moreover, only one subject had a 5-year risk, and only 7 subjects a 10-year risk above or equal to 10% (min 10%, max 45%).

No differences in terms of GVRS were found between those who discontinued the study drug during follow-up (n=24; mean=7.13, SD=0.93) and those who did not (n=23; mean=7.30, SD=0.88; p=0.406, Mann-Whitney).

Comparison of baseline variables between continuers and discontinuers.

Of the 114 subjects included in the present report, 61 (53.51%) were still on the allocated antipsychotic at 12 months, whereas 53 (46.49%) discontinued study drug. As shown in Figure 8, 33 (62%) discontinued for lack of efficacy, 12 (23%) chose to discontinue on their own initiative, and eight (15%) discontinued for poor tolerability. For 16 (49%) of those who experienced lack of efficacy discontinuing was a clinician's decision, for four (12%) of them it was their own decision, and for 13 (39%) of them it

was a shared decision. For two (25%) of those who experienced poor tolerability it was their own decision, for five (62%) of them it was a shared decision, and for one (13%) of them it was a clinician's decision. Overall, treatment discontinuation was a patient's decision in 18 (34%) cases, a clinician's decision in 17 (32%) cases, and a shared decision in 18 (34%) cases.

All baseline variables displayed in Tables 8, 9, 10 and 11 were compared between those who were still on study drug at one year ("continuers", n=61) and those who did not ("discontinuers", n=53). No differences in terms of sociodemographic or clinical characteristics were found, and illness severity, as measured by GAF and BPRS, was similar between the two groups. Statistical analyses showed no significant differences in any comparison (Mann-Whitney, $p>0.05$ for all comparisons).

	NOMAS Cohort (n=2,737) [74]	GiSAS sample (n=47)
Age (yrs), mean (SD)	68.8 (10.4)	49.34 (8.1)
Sex		
Men	1,006 (36.8)	24 (51)
Women	1,731 (63.2)	23 (49)
Hispanic	1,443	0 (0)
Black	681	0 (0)
White	546	47 (100)
Behavioral		
Moderate alcohol consumption	929 (34.0)	7 (14.9)
Former smoking	954 (34.9)	19 (40.4)
Current smoking	491 (18.0)	19 (40.4)
Moderate-to-heavy physical activity	237 (8.7)	5 (10.6)
Cardiovascular		
Systolic BP (mm Hg), mean (SD)	143 (21)	127 (14)
Diastolic BP (mm Hg), mean (SD)	83 (11)	81 (7)
Fasting blood sugar (mg/dl), mean (SD)	104.6 (47.4)	92.0 (51.2)
Diabetes	552 (20.2)	0 (0)
Waist circumference (cm), mean (SD)	92.9 (12.7)	96.7 (16.0)
Peripheral vascular disease	354 (12.9)	0 (0)
Antihypertensive medications	1,089 (40.3)	581 (40.9)
Total cholesterol (mg/dl), mean (SD)	203 (40)	207 (87)
HDL (mg/dl), mean (SD)	47 (15)	44 (11)

Values are presented as n (%) unless otherwise indicated. BP = blood pressure; HDL = high-density lipoprotein; NOMAS = Northern Manhattan Study; GiSAS= Italian Group for the Study of Second Generation Antipsychotics.

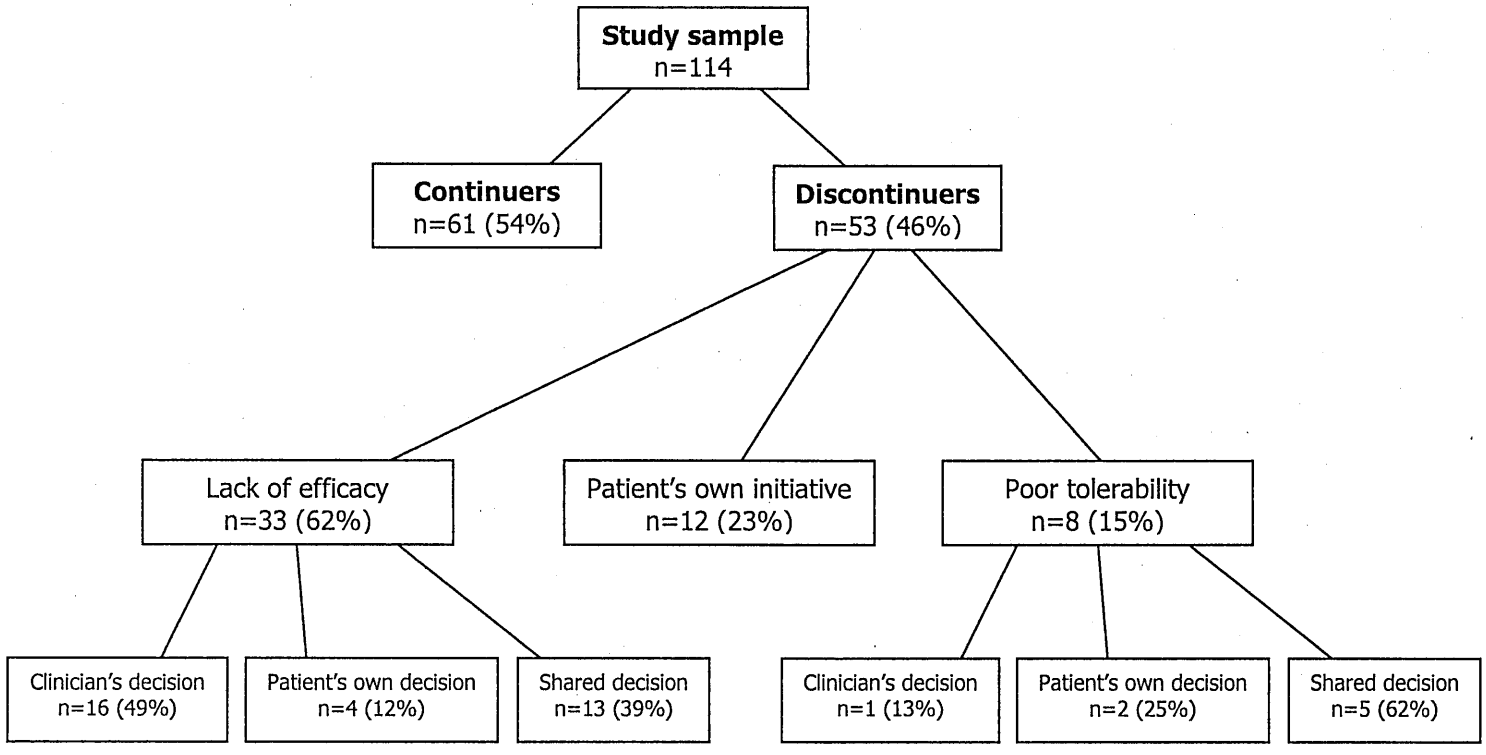
Table 12. Variables for the calculation of the global vascular risk score (GVRS): baseline Characteristics of the NOMAS Cohort and of the GiSAS sample.

	5-Year Risk				10-Year Risk			
	<5%	**5% to 10%**	**10% to 20 %**	**>20%**	**<5%**	**5% to 10%**	**10% to 20%**	**>20%**
N (%)	42 (89%)	4 (9%)	1 (2%)	-	26 (55%)	14 (30%)	6 (13%)	1 (2%)
GVRS*, mean (SD)	7.01 (0.69)	8.67 (0.13)	9.87 (-)	-	6.55 (0.43)	7.69 (0.16)	8.51 (0.26)	9.87 (-)

*Global Vascular Risk Score

Table 13. 5- and 10-Year cardiovascular risk prediction with the NOMAS GVRS (n=47).

Figure 8. Main reasons for drug discontinuation of the first 114 patients enrolled in the GiSAS trial.



Subjects not on antipsychotic medication at study entry (n=14) were excluded from the analysis on the antipsychotic-induced side effects assessed through the LUNSERS. Only one difference of borderline statistical significance was found. Discontinuers had higher scores than continuers in the extrapyramidal symptom subgroup (mean=5.50, SD=4.52 vs. mean=3.69, SD=3.56; Mann-Whitney, p=0.049). Comparisons showed no statistically significant differences in any other subgroup of adverse effects (Mann-Whitney, p>0.05 for all comparisons).

Comparisons between the two groups in terms of baseline levels of metabolic syndrome variables or prolactin and of anthropometric indicators of obesity were performed. Only one statistically significant difference was found. Discontinuers had lower levels of fasting HDL (mean=23.40, SD=20.21) if compared with continuers (mean=31.89, SD=22.51; Mann-Whitney, p=0.024). No other comparison showed statistical significance (Mann-Whitney, p>0.05 for all comparisons).

Data from physical examination and ECG were compared between the two groups, as well. No significant differences in terms of electrocardiographic abnormalities, extrapyramidal symptoms or clinical signs of hyperprolactinemia were found (Chi-Square, p>0.05 for all comparisons).

Comparison of follow-up variables between continuers and discontinuers.

For 39 subjects (34%) follow-up LUNSERS and GAF scores were missing. Thus, they were not included in the present analysis. No differences in terms of baseline variables were found between subjects with missing data (n=39) and the rest of the sample (n=75) (Mann-Whitney, p>0.05 for all comparisons). Eight (20.5%) of the excluded subjects and 14 (18.7%) of the included subjects fulfilled at least three criteria of metabolic syndrome at baseline (centralized analyses).

33 subjects (44.0%) discontinued study drug at follow-up, whereas 42 (56%) did not. Tables 14 and 15 show the mean LUNSERS and GAF scores, with the mean differences and effect sizes (ES), at three time points: at baseline (BL, all subjects: n=75), when the assigned medication is stopped or changed (FU1, only discontinuers: n=33), and at 12 months (FU2, all subjects: n=75).

Both continuers and discontinuers showed statistically significant improvements in GAF scores at 12 months (Wilcoxon, $p<0.01$). Although there was no statistically significant difference between continuers and discontinuers in terms of 12-month GAF ratings (Mann-Whitney, $p>0.05$), a significant difference in terms of magnitude of change was found, continuers showing greater improvement at FU2 (Mann-Whitney, $p=0.037$) with a moderate and statistically significant effect size (0.62, 95% IC 0.18/1.06).

For discontinuers the size of change before and after treatment discontinuation differed. The change in mean GAF scores from BL to FU1 showed an effect size of 0.15 (95% IC -0.33/0.64), whereas the change from FU1 to FU2 showed an effect size of 0.27 (95% IC -0.21/0.76). Moreover, only the improvement registered from FU1 to FU2 reached statistical significance (Wilcoxon, $p=0.050$).

At 12 months (FU2-BL) continuers showed a statistically significant reduction of LUNSERS total score (Wilcoxon, $p<0.0001$). Moreover, they showed significant reductions in the mean ratings of the following LUNSERS subgroups of adverse effects: psychic symptoms ($p<0.0001$, ES: -0.64, 95% IC -1.08/-0.20), autonomic symptoms ($p=0.014$), and endocrine symptoms ($p=0.011$). On the contrary, discontinuers did not show any significant improvement in self-reported side effects (Wilcoxon, $p>0.05$ for all comparisons).

Comparisons between continuers and discontinuers at 12 months showed statistically significant differences in LUNSERS total score (Mann-Whitney, $p=0.026$) and in the following subgroups of adverse effects: extrapyramidal symptoms ($p=0.047$), psychic

symptoms (p=0.034), autonomic symptoms (p=0.028), and endocrine symptoms (p=0.020). However, no statistically significant differences were found in terms of magnitude of change (Mann-Whitney, p>0.05 for all comparisons).

Figure 9 shows a list of evidence-based interventions for promoting compliance with the assigned treatment (see APPENDIX 5). Table 16 shows the percentages of continuers and discontinuers who received those interventions during the one-year follow-up. Most of the sample received interventions specifically aimed at improving therapeutic alliance (91%), behavioural interventions (95%) and social or family support strategies (69%). Few subjects received specific psychotherapy (15%) and individual psycho-education (19%) and no one received group psycho-education. Less than half of the sample was involved in organisational strategies aimed at improving adherence to treatment prescriptions (45%) and, among them, no one received an integrated treatment for schizophrenia and substance abuse. Continuers and discontinuers were compared in terms of the types of intervention received. No statistically significant differences emerged (Chi Square, p>0.05 for all comparisons).

LUNSERS subgroups of adverse effects	Mean BL (SD)*	Mean FU1 (SD)**	Mean FU2 (SD)*
Extrapyramidal	**4.64 (4.24)**	**5.39 (4.06)**	**4.15 (3.81)**
Muscle stiffness	0.64 (0.99)	0.94 (1.06)	0.72 (1.06)
Slowing of movements	0.97 (1.21)	1.03 (1.02)	1.07 (1.08)
Muscle spasm	0.47 (0.74)	0.39 (0.70)	0.29 (0.59)
Restlessness	1.24 (1.1)	1.42 (1.25)	1.00 (0.97)
Shakiness	0.59 (0.95)	0.70 (0.98)	0.48 (0.78)
Involuntary movements	0.33 (0.68)	0.39 (0.83)	0.23 (0.45)
Drooling mouth	0.40 (0.79)	0.52 (0.79)	0.36 (0.73)
Psychic	**12.33 (5.78)**	**11.39 (5.96)**	**9.55 (5.83)**
Difficulty staying awake	1.01 (0.98)	0.79 (0.86)	0.69 (0.82)
Increased dreaming	0.65 (0.92)	0.55 (0.87)	0.41 (0.749
Difficulty in concentrating	1.61 (1.08)	1.45 (0.97)	1.35 (0.98)
Tension	1.40 (1.01)	1.33 (1.19)	1.03 (0.96)
Tiredness	1.60 (0.88)	1.52 (0.91)	1.33 (0.93)
Difficulty in remembering	1.37 (1.09)	1.36 (0.96)	1.21 (1.03)
Lack of emotions	1.04 (1.10)	0.91 (1.01)	0.91 (1.04)
Depression	1.32 (1.02)	1.27 (1.01)	0.93 (1.02)
Sleeping too much	1.25 (1.05)	1.15 (1.06)	0.95 (0.90)
Difficulty getting to sleep	1.07 (0.92)	1.06 (1.09)	0.73 (0.88)
Allergic	**1.44 (2.02)**	**1.03 (1.62)**	**1.18 (1.94)**
Rash	0.28 (0.63)	0.30 (0.64)	0.23 (0.53)
Sensitivity to sun	0.57 (0.92)	0.30 (0.68)	0.40 (0.77)
Unusual skin marks	0.15 (0.46)	0.18 (0.77)	0.21 (0.70)
Itchy skin	0.44 (0.81)	0.39 (0.70)	0.40 (0.73)
Anticholinergic	**2.68 (2.91)**	**2.18 (2.42)**	**2.25 (2.38)**
Dry mouth	0.77 (0.99)	0.85 (1.18)	0.67 (1.02)
Constipation	0.88 (1.15)	0.79 (1.14)	0.76 (1.01)
Difficulty passing water	0.20 (0.59)	0.09 (0.29)	0.19 (0.46)
Blurred vision	0.51 (0.91)	0.24 (0.50)	0.39 (0.68)
Passing a lot of water	0.32 (0.77)	0.21 (0.54)	0.25 (0.57)
Other autonomic	**2.63 (2.64)**	**3.00 (3.06)**	**2.24 (2.95)**
Dizziness	0.47 (0.70)	0.48 (0.87)	0.44 (0.83)
Feeling sick	0.39 (0.69)	0.58 (0.87)	0.31 (0.66)
Palpitations	0.80 (0.91)	0.79 (0.93)	0.57 (0.82)
Increased sweating	0.76 (1.08)	1.00 (1.12)	0.63 (1.06)
Diarrhea	0.21 (0.47)	0.15 (0.36)	0.29 (0.71)
Endocrine	**3.00 (3.34)**	**2.70 (3.21)**	**2.13 (3.12)**
Swollen or tender chest	0.25 (0.62)	0.27 (0.63)	0.11 (0.42)
Period problems	0.44 (0.92)	0.45 (0.90)	0.33 (0.83)
Increased sex drive	0.41 (0.89)	0.52 (0.91)	0.33 (0.66)
Difficulty achieving climax	0.83 (1.29)	0.39 (1.00)	0.48 (1.04)
Reduced sex drive	0.73 (1.20)	0.79 (1.22)	0.67 (1.14)
Periods less frequent	0.33 (0.87)	0.27 (0.67)	0.21 (0.70)
Others reactions	**2.59 (2.12)**	**2.88 (2.07)**	**2.2 (1.92)**
Headaches	0.73 (0.89)	0.73 (0.91)	0.57 (0.81)
Loosing weight	0.43 (0.77)	0.52 (0.83)	0.28 (0.63)
Putting on weight	1.11 (1.20)	1.30 (1.55)	0.99 (1.22)
Pins and needles	0.32 (0.57)	0.33 (0.54)	0.36 (0.56)
"Red herring" items	**3.28 (3.80)**	**3.33 (4.40)**	**2.92 (4.21)**
Total score	**29.31 (12.27)**	**28.73 (18.67)**	**23.76 (18.40)**

*n=75; **n=33

Table 14. Mean change in LUNSERS scores of those who discontinued study drug (n=33) and those who did not (n=42).

		BL	FU1	FU2	Change FU1-BL		Change FU2-FU1		Change FU2-BL	
		Mean (SD)	Mean (SD)	Mean (SD)	Mean Δ	ES (95% CI)[†††]	Mean Δ	ES (95% CI)[†††]	Mean Δ	ES (95% CI)[†††]
Extrapyramidal	**Continuers[†]**	3.79 (3.52)	-	3.45 (3.62)	-	-	-	-	-0.33 (2.60)[ns]	-0.09 (-0.52/0.33)
	Discontinuers[††]	5.73 (4.84)	5.39 (4.06)	5.03 (3.92)	-0.33 (3.56)[ns]	-0.08 (-0.56/0.41)	-0.36 (2.62)[ns]	-0.09 (-0.57/0.39)	-0.70 (3.23)[ns]	-0.16 (-0.64/0.33)
Psychic	**Continuers[†]**	11.95 (5.73)	-	8.21 (5.83)	-	-	-	-	-3.74 (4.95)[§§]	-0.64 (-1.08/-0.20)
	Discontinuers[††]	12.81 (5.89)	11.39 (5.96)	11.24 (5.45)	-1.42 (5.68)[ns]	-0.24 (-0.72/0.25)	-0.15 (4.05)[ns]	-0.03 (-0.51/0.46)	-1.58 (4.87)[ns]	-0.27 (-0.76/0.21)
Allergic	**Continuers[†]**	1.24 (1.63)	-	1.02 (2.02)	-	-	-	-	-0.21 (1.66)[ns]	-0.12 (-0.55/0.31)
	Discontinuers[††]	1.70 (2.43)	1.03 (1.62)	1.37 (1.84)	-0.47 (1.46)[ns]	-0.32 (-0.81/0.16)	0.34 (1.40)[ns]	0.19 (-0.29/0.68)	-0.12 (1.91)[ns]	-0.15 (-0.63/0.33)
Anticholinergic	**Continuers[†]**	2.45 (2.30)	-	1.83 (2.28)	-	-	-	-	-0.62 (1.97)[ns]	-0.27 (-0.70/0.16)
	Discontinuers[††]	2.97 (3.57)	2.18 (2.42)	2.79 (2.43)	-0.79 (2.87)[ns]	-0.26 (-0.74/0.23)	0.61 (1.77)[ns]	0.25 (-0.24/0.73)	-0.18 (2.79)[ns]	-0.06 (-0.54/0.42)
Other autonomic	**Continuers[†]**	2.59 (2.67)	-	1.74 (2.66)	-	-	-	-	-0.86 (2.01)[§§]	-0.32 (-0.75/0.11)
	Discontinuers[††]	2.67 (2.64)	3.00 (3.06)	2.88 (3.22)	0.33 (2.94)[ns]	0.11 (-0.37/0.60)	-0.12 (1.76)[ns]	-0.04 (-0.52/0.44)	0.21 (2.47)[ns]	0.07 (-0.41/0.55)
Endocrine	**Continuers[†]**	2.62 (2.81)	-	1.59 (2.89)	-	-	-	-	-1.02 (2.81)[§§]	-0.36 (-0.79/0.07)
	Discontinuers[††]	3.48 (3.91)	2.70 (3.21)	2.82 (3.32)	-0.79 (2.62)[ns]	-0.22 (-0.70/0.27)	0.12 (1.19)[ns]	0.04 (-0.45/0.52)	-0.67 (2.68)[ns]	-0.18 (-0.66/0.30)
Others reactions	**Continuers[†]**	2.48 (1.86)	-	1.95 (1.74)	-	-	-	-	-0.52 (1.55)[ns]	-0.29 (-0.72/0.14)
	Discontinuers[††]	2.73 (2.44)	2.88 (2.07)	2.51 (2.11)	0.15 (2.48)[ns]	0.07 (-0.42/0.55)	-0.36 (1.45)[ns]	-0.17 (-0.66/0.31)	-0.21 (2.43)[ns]	-0.10 (-0.58/0.39)
LUNSERS tot	**Continuers[†]**	27.12 (14.78)	-	19.81 (17.05)	-	-	-	-	-7.31 (9.76)[§§]	-0.45 (-0.89/-0.02)
	Discontinuers[††]	32.09 (19.89)	28.73 (18.67)	28.79 (19.07)	-3.36 (14.86)[ns]	-0.17 (-0.66/0.31)	0.06 (9.87)[ns]	0.00 (-0.48/0.49)	-3.30 (13.87) [ns]	-0.17 (-0.65/0.32)
GAF	**Continuers[†]**	49.31 (17.05)	-	60.02 (17.08)	-	-	-	-	10.71 (14.17)[§§]	0.62 (0.18/1.06)
	Discontinuers[††]	47.27 (14.37)	49.54 (15.13)	53.85 (16.00)	2.27 (11.65)[ns]	0.15 (-0.33/0.64)	6.58 (13.11)[§]	0.27 (-0.21/0.76)	4.30 (11.32)[§§,▪]	0.43 (-0.06/0.92)

Grey background indicates statistically significant cross-sectional comparisons between continuers and discontinuers (Mann-Whitney, $p<0.05$);
ns= not significant; [†]n=42; [††]n=33; [†††]Bias corrected (Hedges) effect size; [§]Wilcoxon, $p<0.05$; [§§]Wilcoxon, $p<0.01$;
[▪]statistically significant difference of the magnitude of change between continuers and discontinuers (Mann-Whitney test, $p<0.05$).

Table 15. Change in the GAF and LUNSERS scores of those who discontinued study drug (n=33) and of those who did not (n=42).

Figure 9. Activities for promoting compliance with the assigned treatment.

1. STRATEGIES FOR IMPROVING THE THERAPEUTIC ALLIANCE

A) Has the patient's personal experience and his/her subjective perception of both the beneficial and undesired effects of the AP treatment been investigated? YES NO

B) Have the goals of the AP treatment been shared with the patient? YES NO

C) Has the patient been involved in planning and monitoring the AP therapy? YES NO

2. BEHAVIOURAL INTERVENTIONS

A) for improving attendance of follow-up examinations

A1) Has the patient received regular telephone or mailed reminders? YES NO

A2) Has the patient been permitted to come for visits even without an appointment? YES NO

A3) Has the patient been provided with guidance brochures? YES NO

A4) Have the procedures for accessing the service been negotiated with the patient? (e.g. appointments always at the same time and on the same day of the week) YES NO

B) for improving daily compliance with the prescribed treatment

B1) Has the dosage been optimised and the manner of taking the doses simplified? YES NO

B2) Has the treatment been delivered to the patient in a loose form or in a customised pack? YES NO

B3) Has the treatment been administered directly to the patient by a staff member? YES NO

B4) Has administration of the treatment been entrusted to a family member? YES NO

3. PSYCHO-EDUCATIONAL INTERVENTIONS

Has a psycho-educational activity been conducted with regard to compliance with AP treatment?

3A) Individual YES NO

3B) Group YES NO

4. PSYCHOTHERAPY

Has a psychotherapeutic activity been conducted to improve the patient's motivation and insight?

4A) cognitive YES NO

4B) short psychodynamic YES NO

4C) motivational therapy YES NO

5. SOCIAL AND FAMILY SUPPORT STRATEGIES

A) Have the patient's family been involved in planning and monitoring the AP treatment? YES NO

B) Have the goals of the pharmacological treatment been shared with the patient's family? YES NO

C) Has a family psycho-educational activity been conducted? YES NO

D) Have specific activities been conducted to improve the patient's social network? YES NO

6. ORGANISATIONAL STRATEGIES

A) When the patient was discharged from hospital or residential facility, was he/she placed in contact with the community mental health team? YES NO

B) Has an integrated treatment for both schizophrenia and substance abuse been implemented? YES NO

	1. THERAPEUTIC ALLIANCE				2. BEHAVIOURAL INTERVENTIONS			3. PSYCHO-EDUCATIONAL INTERVENTIONS			4. PSYCHOTHERAPY	5. SOCIAL SUPPORT STRATEGIES					6. ORGANISATIONAL STRATEGIES		
	A	B	C	All types	A	B	All types	A	B	All types[†††]	All types	A	B	C	D	All types	A	B	All types
CONTINUERS[†], Yes	34 (81.0)	40 (95.2)	39 (92.9)	40 (95.2)	41 (97.6)	39 (92.9)	41 (97.6)	4 (9.5)	0 (0.0)	8 (19.0)	5 (11.9)	15 (35.7)	24 (57.1)	3 (7.1)	15 (35.7)	31 (73.8)	16 (38.1)	0 (0.0)	16 (38.1)
DISCONTINUERS[††], Yes	24 (72.7)	28 (84.8)	26 (78.8)	28 (84.8)	30 (90.9)	29 (87.9)	30 (90.9)	5 (15.2)	0 (0.0)	6 (18.2)	6 (18.2)	18 (54.5)	17 (51.5)	3 (9.1)	8 (24.2)	21 (63.6)	18 (54.5)	0 (0.0)	18 (54.5)
TOTAL, Yes	58 (77.3)	68 (90.7)	65 (86.7)	68 (90.7)	71 (94.7)	68 (90.7)	71 (94.7)	9 (12.0)	0 (0.0)	14 (18.7)	11 (14.7)	33 (44.0)	41 (54.7)	6 (8.0)	23 (30.7)	52 (69.3)	34 (45.3)	0 (0.0)	34 (45.3)

Values are presented as n (%) unless otherwise indicated; see Figure 8 for the description of the various types of intervention; for discontinuers only interventions delivered before treatment discontinuation are considered.
[†]n=42; [††]n=33; [†††]For 5 subjects data on type of psycho-education were missing; *p<0.05, **p<0.01 (Chi-Square Test).

Table 16. Activities for promoting compliance with the assigned treatment received by those who discontinued study drug and by those who did not (n=75).

Discussion

We performed the present analysis to explore the baseline characteristics of the first 114 subjects included into the trial and to identify differences between those who discontinued study drugs at follow-up and those who did not. The purpose of this preliminary analysis was to test the convergent validity of all-cause treatment discontinuation as an endpoint for effectiveness. Thus, the assumption that discontinuers were on worse clinical conditions at the time they stopped the assigned antipsychotic was put under scrutiny.

Most of the first 114 subjects included into the trial were relatively young schizophrenic outpatients and had a moderate-to-severe illness severity and few medical comorbidities. The majority showed an enough positive attitude towards antipsychotic therapy, with 76% of the sample reporting a low burden of antipsychotic induced side-effects as measured by LUNSERS scale, and only 15% reporting a complete dissatisfaction with past antipsychotic medication. Compliance with previous antipsychotic prescriptions was rated as satisfactory by the treating psychiatrists in most of the patients (63%).

For 47 subjects of the sample, who were at least 40 years of age, we were able to calculate ten-year cardiovascular risk adopting a model which included behavioural and anthropometric factors. The results of this calculation are consistent with the other findings presented here. Most of the subjects had a low cardiovascular risk, with 55% of the sample showing both a 5- and a 10-year risk below 5%. The inclusion of anthropometric and behavioural risk factors in this prediction model opened up the doors to the cardiovascular risk assessment of relatively young subjects [74]. However, the lower age limit (≥40 years) for risk calculation represents a major obstacle to the adoption of the GVRS as an outcome indicator in people affected by schizophrenia.

46% of the subjects included in the present report discontinued the allocated antipsychotic during the one-year follow-up. Most of them (62%) discontinued for lack of efficacy. In about one third of them discontinuation was a patient's decision, in another third it was a clinician's decision, and it was a shared decision in the last third. No statistically significant differences were found between continuers and discontinuers in terms of baseline clinical and sociodemographic variables. There were, however, some significant differences between the two groups in terms of outcome variables. Even if both groups showed statistically significant improvements in GAF scores at 12 months, continuers showed a greater magnitude of improvement with a moderate and statistically significant effect size. Moreover, only continuers showed statistically significant improvements in self-reported side effects with a moderate and statistically significant effect size for psychic symptoms.

There are some limitations which should be taken into account in the interpretation of these results. This analysis is based on observational data and is therefore potentially subject to bias. Noteworthy is the substantial amount of missing data. We assumed that all missing data were missing completely at random thus we opted for case deletion [149]. The validity of this assumption, however, could not be properly evaluated. Owing to missing data and to the difficulties encountered in trial's recruitment we could perform the analysis of follow-up variables for only 75 subjects. The small sample did not allow us to identify factors associated to treatment discontinuation through a more complex multivariate statistical analysis. Finally, as only discontinuers had an intermediate follow-up (FU1), we were not able to compare their condition at drug discontinuation with that of a reference or control group.

The sample population for a pragmatic trial must be representative of the type of patients who might be offered the treatment in real-world conditions. We have made all efforts to avoid selecting unrepresentative patients, and, in fact, the

sociodemographic and clinical characteristics of our sample are very similar to those of observed in other naturalistic samples of patients attending Italian community mental health services [150]. However, since the study focused on antipsychotic side-effects and since it recruited only subjects without metabolic syndrome and diabetes, a selection of particularly healthy subjects could have occurred.

Although all subjects had been screened negative for metabolic syndrome by the study investigators, 22 (19%) of them, recruited in 11 study centres, showed positive results to central blood tests. For seven of those subjects we were able to retrieve the results of the screening tests performed at the respective study centers, and we found them negative. As the study investigators had to rely on their own tests and examinations to opt for inclusion, we concluded that the screening of those subjects had been done properly. Discordance between local and central laboratory tests can be attributed to methodological factors or to the fact that blood samples for local and central analyses had been taken at different times. Future efforts will focus on carefully checking out these discrepancies in order to identify errors in patient inclusion.

In our study premature treatment discontinuation was mostly due to lack of efficacy, which is consistent with previous findings [128, 129, 151]. Perkins et al. (2008) conducted a study aimed at evaluating predictors of treatment discontinuation among 400 first-episode patients randomly assigned to olanzapine, quetiapine, or risperidone as part of a 52-week, randomized, double-blind, flexible-dose, multicenter study (the CAFE study) [151, 152]. 115 patients who discontinued treatment against medical advice were compared with 119 patients who completed the study. Poor treatment response and low medication adherence were independent and significant predictors of discontinuation against medical advice. Ongoing substance abuse, ongoing depression, and treatment response failure significantly predicted poor medication compliance. Higher cognitive performance at baseline and black ethnicity were associated with

lower medication compliance. The study demonstrated the importance of treatment response in predicting discontinuation against medical advice and poor adherence to medication, and supported interventions to improve behaviours linked with adherence, particularly by targeting substance use disorders and depressive symptoms [151].

One-year treatment discontinuation rate (46.49%) in our sample was lower than those reported in similar RCTs like the CATIE (74%) and the CAFE study (70.25%), but it was consistent with that reported in the EUFEST trial (41.57%) [21, 27, 152] . The agreement between our discontinuation rate and that reported by Kahn et al. (2008) could be explained by the fact that both studies were conducted in Europe, whereas CAFE and CATIE were conducted in the United States. Thus, we can hypothesize that the psychosocial interventions received by people involved in GiSAS and in EUFEST trial, and especially those linked with treatment adherence, were similar and differed from those received by people recruited in CAFE and CATIE trial.

No significant differences between continuers and discontinuers were found in terms of baseline burden of antipsychotic induced side-effects, in terms of compliance with previous antipsychotic prescriptions or in terms of the interventions for promoting treatment adherence received during follow-up. Therefore, treatment discontinuation cannot be attributed to predisposing factors or to a worse quality of treatment.

The fact that no subject received a targeted intervention for alcohol or substance abuse is consistent with the fact that none was affected by those disorders. On the other hand, the fact that 31% of those who were discharged from hospital during the study period were not placed in contact with community mental health teams can be interpreted as an indicator of low treatment quality. Immediate delivery of community care should, in fact, represent a key goal of any mental health care system in which hospital stay is generally short, as is the case in Italy. This finding, however, is not surprising. In a recent study we estimated the symptomatic outcome of a

representative sample of 206 patients admitted for short treatment to 64 general hospital psychiatric units in Italy [145]. The majority of the sample (71%, N=147) was discharged home and this was considered for most patients the best option by the treating clinician. Nevertheless, discharge and aftercare planning were discussed and agreed with the community teams only for about half the sample (55%, n=113) [145]. The assumption that discontinuers were on worse clinical conditions at the time they stopped the assigned antipsychotic is only partially supported by our results. Discontinuers had a worse outcome than those who were on the assigned medication at follow-up. Overall, however, the differences between these two groups were not striking. Moreover, differences in outcome were mainly due to self reported side-effects and less to efficacy. One interesting finding is, in fact, that not only continuers but also discontinuers significantly improved at follow-up in terms of GAF scores. For discontinuers, however, the size of change differed before and after treatment discontinuation and only the improvement registered from FU1 to FU2 reached statistical significance. One possible explanation is that the change of medication which followed treatment discontinuation accounted for this improvement. If this interpretation were correct it would support the assumption that treatment discontinuation coincided with a perceived failure of the allocated monotherapy.

CHAPTER IV

CONCLUSIONS

The thesis specifically focused on the background, rationale and design of the GiSAS trial, on its planning and conduct, and on the preliminary analysis of the first 114 followed-up subjects.

The trial encountered significant problems in patients recruitment which caused a big delay in the project deadline. We originally planned to recruit about 800 patients over a two-year period but we ended up recruiting 300 patients over 45 months. Evidently, we planned to recruit an unrealistically large number of patients in an unrealistically tight time frame. Also the involvement of the study centers took much more time than expected. We originally aimed at recruiting 50 participating centres but, as time passed, the target appeared beyond reach. The delay in this process was mainly due to clerical reasons as ethics boards approval had to be obtained for each participating center separately. Finally, in fact, only 35 Italian mental health services participated. The investigators' lack of commitment to study recruitment and conduct was another major problem which has been only partially tackled by the remedial actions previously described. Their passive attitude towards every aspect of study implementation proved to be hardly modifiable and more pervasive than expected.

The second part of the thesis delved into the concept of outcomes using a secondary analysis of existing data and a preliminary analysis of GiSAS trial data.

In a secondary analysis of pharmaco-epidemiological data, persistence was adopted as an endpoint for effectiveness to check out whether the established lack of efficacy of reboxetine would have been translated into a higher proportion of treatment discontinuations for any cause if compared to SSRIs. The results added validity to the assumption that differences in discontinuation rates reflect differences in effectiveness in actual clinical practice.

In the preliminary analysis of the first 114 included subjects we investigated some aspects of the validity of the two primary endpoints of the trial: metabolic syndrome

and treatment discontinuation. As we were still blinded and we did not know the drug to which each subject was randomized we were not able to compare intervention groups. We calculated patients' cardiovascular risk adopting a model which included behavioural and anthropometric factors. Most of the subjects showed a low cardiovascular risk, and this result was consistent with the aim of recruiting subjects without metabolic abnormalities. The GVRS showed to be a promising outcome indicator. However, its use in people affected by schizophrenia is questionable because of its lower age limit (40 years). We compared continuers and discontinuers both in terms of baseline and follow-up data. Results showed that discontinuers had a worse outcome than those who were on the assigned medication at follow-up. Overall, however, the differences between these two groups were mainly attributable to self reported side-effects. Thus, the assumption that discontinuers were on worse clinical conditions at the time they stopped the assigned antipsychotic was only partially supported by our results.

Some critical issues of the trial design have to be highlighted. In chapter 2, page 57, the trial's recruitment flow was described. In the first nine months of the study patient inclusion was very low: out of 371 screened subjects only 34 (9%) were randomized. Thus, there was a significant degree of participants' selection. Figure 4 (page 63) shows reasons for exclusion of the first 337 excluded subjects. The change of the current antipsychotic medication was by far the most indicated reason for exclusion (59%). Notwithstanding the attempts to move towards pragmatic inclusion, many people were screened not eligible and this could have repercussions on how generalizable the findings are or are not. However, clinical reasons such as "not having a condition appropriate for changing medication" (Reason 1), or "one of the study drugs is known to be ineffective or intolerable" (Reasons 5, 6, 7) or "it is unlikely that the subject can be followed-up for the whole study period" (Reason 8) accounted for

75% of the exclusions (see Figure 4, page 63). If those exclusions were not taken into account, 71% of the eligible subjects would be excluded and 29% of them would be included. In this regard, I can cite the following example: Davies et al. (2007) observed that only 20–37% of possibly eligible patients (those with a diagnosis of schizophrenia whose drug treatment was being changed owing to poor response or intolerance) were randomised into the CUtLASS trial and that the remaining patients were either not referred or refused to participate [26]. Again, if we had considered for elegibility, like CUtLASS investigators did, only those with a diagnosis of schizophrenia whose drug treatment was being changed, 80% of the eligible subjects would have been excluded and 20% of them would have been included (see Figure 4, page 63).

We have extended the screening for elegibility to all subjects above age with a clinical diagnosis of schizophrenia attending one of the participant centers. The hyperinclusivity of our screening might therefore have contributed to the observed significant degree of participants' selection. However, the above cited revisited proportions of included subjects (20-29%) might reassure about the inclusivity of our study and about the representativeness and the applicability of our findings.

Given the controversy on the comparative efficacy of FGAs over SGAs, we had hypothesized that clinicians would have faced substantial uncertainty in the choice of the antipsychotic likely to provide greatest clinical benefit in adult patients who had responded inadequately to previous antipsychotic medication. This hypothesis however was not confirmed by the results of the GiSAS survey which showed a preference for SGAs. This lack of uncertainty might have had a negative impact on trial's implementation, especially because, through the introduction of a specific inclusion criterion, uncertainty had been adopted as the leading criterion for recruitment.

In chapter 1, page 15, the concepts of equipoise and uncertainty have been presented and discussed. Notwithstanding some criticisms [45, 46] most of the cited authors

believed that the ethical basis for planning a pragmatic trial should rely on equipoise. Equipoise has both been described as the ethical basis of randomized clinical trials and as a way to make principles of care compatible with those of clinical research [30-44]. However, most of the clinical trials being conducted are industry-sponsored and commercial support is obviously not dependant on equipoise. Fries and Krishnan (2004) formulated an interesting concept that accounted for the surplus of positive industry-sponsored RCTs evaluating new drugs [46]. They reported that all 45 of the industry sponsored RCTs presented over one year at the meetings of the American College of Rheumatology favoured the drug of the sponsor and postulated that the most important reason for these results was 'design bias' [46]. From an industrial perspective the drug development process must necessarily involve 'designing for success'. This is possible given all prior information and the extensive preliminary scientific work and investments, including preliminary trials to evaluate efficacy [46]. If equipoise was the only ethical principle we can lean upon, we were brought to believe that most of the available scientific evidence is unethical. It follows that other principles are involved in randomized clinical research and that there must be room for considering ethical at least some of them. For Fries and Krishnan (2004), for instance, 'design bias' was not necessarily a bad thing. As they considered violation of equipoise essential to efficient medical progress they rejected the principle itself. They suggested that the paternalistic and outdated concept of equipoise should be replaced by better alternatives such as the 'positive expected value of participation'. This concept holds that the principle of 'equal uncertainty' should be replaced by the principle of a reasonable 'expected value' for the participants after pooling the expected results of the trial's arms. For example, if a new drug expected to yield a response rate around 40% is compared to a standard treatment known to have a response rate of 20%, each participant before randomization should have a pooled expected value of 30%.

This expected value is better than standard treatment. Therefore, it can be assumed as ethical justification for planning a clinical trial and it gives reasons for trial participation [46]. The concept of 'positive expected value of participation' overcomes the internal contradictions of equipoise and the paradox that it generates. Moreover, it is more consistent with the settled practice of formulating study hypotheses. Trialists, in fact, are usually required to formulate a prediction about the relative efficacy of the tested interventions and this would again be in some contradiction with the principle of equipoise. The positive value of participation to the GiSAS trial was mainly expected in terms of tolerability. As tolerablity was not reported to be the leading criterion for antipsychotic prescription or for changing medication (see GiSAS Survey) even from this perspective we can account for the difficulties encountered in trial's recruitment.

Another critical aspect of trial's implementation was represented by the baseline diagnosis of metabolic syndrome. There were, in fact, some discrepancies between the evaluation performed at inclusion by the investigators and the one performed by the study group after central blood tests. These discrepancies could be attributed to errors in patients recruitment. However, a specific characteristic of the trial design could also be implicated. As stated above (see page 30), the present trial was designed within the pragmatic-explanatory continuum. Thus, its protocol combined features belonging to both extremes of the spectrum. The fact that the investigators were completely in charge of patient inclusion was a 'pragmatic' characteristic of the trial. On the other hand, the choice of diagnosing metabolic syndrome through central blood analyses was motivated by an 'explanatory' need. These two aspects, belonging to different clinical research conceptions, evidently conflicted.

As written on page 44, all analyses will be by full intention-to-treat (ITT) including all randomized participants who will receive at least one dose of investigational drugs. Subjects already taking one of the study drugs at study entry could never be excluded

from the ITT analysis. As clarified further on page 53, inclusion was not determined by the actual intake of the assigned drug. To fulfil our criteria the drug should simply have been prescribed to the patient by the treating clinician in a face-to-face meeting. No specific means of controlling patients' compliance were introduced, thus inclusion was not determined by treatment adherence. The basic ITT principle is that participants should be analyzed in the groups to which they were randomized, regardless of whether they received or adhered to the allocated intervention and regardless of whether they withdrew from the trial. We decided to link patients' inclusion not only to randomization but also to the prescription of the allocated treatment and this is not perfectly in line with the ITT principle. However, this allowed us to maintain a certain control over the inclusion phase. Through the weekly monitoring of the randomization database we actively prompted clinicians to prescribe the allocated drug. At this stage, dropping out of the trial has not been an easy option for the clinician and it has been considered acceptable only if the patient has withdrawn his/her informed consent. Had we not done so, investigators would have probably not considered randomization as a strong indication but only as a feeble suggestion and many subjects would have received different prescriptions.

Abraha et al. (2010) recently reviewed RCTs that reported using a 'modified' IIT [153]. They identified 475 RCTs and found that the incidence of such trials significantly increased for 1982 to 2002. The descriptions of the modified IIT approaches were found to be ambiguous and covering any type of descriptions for exclusion, such as missing data and deviation from protocol. They classified types of IIT deviations into six categories, the first of which was treatment- related and concerned the fact of having received or not at least one dose of study drug. The authors concluded that explicit statements about post-randomization exclusions should replace the ambiguous terminology of modified ITT [154]. We excluded from the full ITT sample four

subjects, three of which because they withdrew their informed consent before the baseline visit and thus they were not prescribed the assigned medication, and one because he/she was involved in an attempt to decipher allocation by the treating clinician (see page 67 for further details). We are aware of the fact that excluding participants is a deviation from the ITT principle, that it might bias results and that even a few exclusions could become relevant when the trial will be considered for meta-analyses. For this reason we plan to perform both a modified (n=296) and a full ITT analysis (n=300).

At page 52 the open nature of the study was only discussed as it was a weakness or a potential source of bias. However, apart from the already mentioned vulnerabilities there are some strengths that deserve to be discussed. What was randomized, after all, was the 'intention to treat' and, in particular, the 'intention to openly treat' with these drugs. The methodological and clinical advantages of this approach should be taken into account.

For RCTs the concept of 'internal validity' refers to the validity of the study results in terms of whether differences in outcomes are related to the allocated treatment. On the other hand, the concept of 'external validity' refers to the transferability of the study results to other populations and settings. A blinded RCT is regarded by most authors as being less subject to bias than an open trial because it minimizes the impact of knowledge of treatment allocation on post-randomized treatment decisions and on outcomes' rating and reporting. As a consequence the internal validity of the findings is considered to be increased. However, a blinded trial is not always feasible and often not appropriate. Moreover, as Beyer-Westendorf and Büller (2011) pointed out, double blinding does not completely prevent from risk of bias in internal validity [154]. Selection bias, for instance, which mainly affects external validity needs to be considered also for internal validity because it might lead to exclude from double-blind

trials subjects who would be considered for participation in open-label trials [154]. The allocation to an open-label medication allows to more closely resemble routine clinical practice increasing the external validity of trial's results. Thus, in some respects, the two trial designs offer complementary strengths and weaknesses [154].

As written above (page 30) pragmatic trials represent an evolution in the direction of enhancing the external validity of experimental design (i.e. the generalizability of the results). The choice to randomize to the intention to 'openly treat' moved our trial toward the pragmatic side of the pragmatic-explanatory spectrum, which was our intent.

In the last four years, the GiSAS study group has been working for the implementation of this multicenter randomized clinical trial. The trial mechanism is now fully functional and working and most of the problems and critical aspects of its implementation have been faced. The trial will finish by mid-2012. As study data are entered as soon as they are collected the first results will be available by end-2012.

MATERIAL PUBLISHED CONTAINING WORK DESCRIBED IN THE THESIS

Barbato A, D'Avanzo B, Ferrannini L, Parabiaghi A, Vaggi M. (2008). [Un'occasione per la ricerca clinica in Italia. Lo studio GiSAS su aripiprazolo, olanzapina e aloperidolo nel trattamento dei disturbi schizofrenici.] Psichiatria di Comunità 7:46-54. [Italian]

Ghio L, Natta W, Barbato A, Marcenaro M, Gotelli S, Jones PB, Parabiaghi A. Schizophrenia Trial Participation: Perceived Inclusion Barriers and Beliefs about Antipsychotics. Pharmacopsychiatry 2011, 44:123-128. **[Table 4 and 5 of the present thesis and APPENDIX 6]**

Parabiaghi A, D'Avanzo B, Tettamanti M, Barbato A, GiSAS Study Group. The GiSAS study: Rationale and design of a pragmatic randomized controlled trial on aripiprazole, olanzapine and haloperidol in the long-term treatment of schizophrenia. Contemp Clin Trials 2011, 32:675-684. **[Table 1 of the present thesis]**

Parabiaghi A, Franchi C, Tettamanti M, Barbato A, D'Avanzo B, Fortino I, Bortolotti A, Merlino L, Nobili A. The declining use of reboxetine in years 2000-2006: a pharmaco-epidemiological comparative study. J Clin Psychopharmacol 2012, 32:303-305. **[Table 1, Figures 1 and 2 of APPENDIX 7]**

CONTRIBUTIONS AND ACKNOWLEDGMENTS

All the material included in the present thesis was autonomously written by me.

I have been in charge of the GiSAS trial development and implementation. The team I directed (GiSAS Study team) included two study monitors and a part-time trial manager. I wrote the protocol and all trial's documents and forms (including the manual of procedures) in collaboration with Angelo Barbato* (Principal Investigator), Barbara D'Avanzo* and Mauro Tettamanti*. I performed the data-management and all statistical analyses of the GiSAS trial data. The GiSAS Survey was carried out in collaboration with the Psychiatric Clinic of the University of Genova. Lucio Ghio** and I contributed equally to the study conception and design. Werner Natta** gave a substantial contribution to the acquisition of data and, with me and Lucio Ghio**, to their analysis and interpretation. The pharmaco-epidemiologic study on reboxetine was conceived and designed by me. I performed the statistical analysis. Carlotta Franchi* contributed to the data acquisition and to the discussion of the results, Mauro Tettamanti* supervised the statistical analysis.

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REFERENCES

1. Adams CE, Awad G, Rathbone J, Thornley B. Chlorpromazine versus placebo for schizophrenia. Cochrane Database Syst Rev 2007:CD000284.

2. Joy CB, Adams CE, Lawrie SM. Haloperidol versus placebo for schizophrenia. Cochrane Database Syst Rev 2006:CD003082.

3. Miyamoto S, Duncan GE, Marx CE, Lieberman JA. Treatments for schizophrenia: a critical review of pharmacology and mechanisms of action of antipsychotic drugs. Mol Psychiatry 2005, 10:79-104.

4. Lahti AC, Lahti RA, Tamminga CA. New neuroleptics and experimental antipsychotics: future roles. In: A. Breier, Editor, *The New Pharmacotherapy of Schizophrenia*, American Psychiatric Press, Washington, DC (1996), pp. 57–87.

5. Hippius H. The history of clozapine. Psychopharmacol Suppl 1989, 99:3-5.

6. Kane J, Honigfeld G, Singer J, Meltzer H. Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. Arch Gen Psychiatry 1988, 45:789-796.

7. Leucht S, Pitschel-Walz G, Abraham D, Kissling W. Efficacy and extrapyramidal side-effects of the new antipsychotics olanzapine, quetiapine, risperidone, and sertindole compared to conventional antipsychotics and placebo. A meta-analysis of randomized controlled trials. Schizophr Res 1999, 35:51-68.

8. Geddes J, Freemantle N, Harrison P, Bebbington P. Atypical antipsychotics in the treatment of schizophrenia: systematic overview and meta-regression analysis. BMJ 2000, 321:1371-1376.

9. Newcomer JW. Abnormalities of glucose metabolism associated with atypical antipsychotic drugs. J Clin Psychiatry Suppl 2004, 18:36-46.

10. Chakos M, Lieberman J, Hoffman E, Bradford D, Sheitman B. Effectiveness of second-generation antipsychotics in patients with treatment-resistant schizophrenia: a review and meta-analysis of randomized trials. Am J Psychiatry 2001, 158:518-526.

11. Tuunainen A, Wahlbeck K, Gilbody S. Newer atypical antipsychotic medication in comparison to clozapine: a systematic review of randomized trials. Schizophr Res 2002, 56:1-10.

12. Leucht S, Corves C, Arbter D, Engel RR, Li C, Davis JM. Second-generation versus first generation antipsychotic drugs for schizophrenia: a meta-analysis. Lancet 2009, 373:31-41.

13. Rummel-Kluge C, Komossa K, Schwarz S, Hunger H, Schmid F, Lobos CA. Head-to-head comparisons of metabolic side effects of second generation antipsychotics in the treatment of schizophrenia: a systematic review and meta-analysis. Schizophr Res 2010, 123:225-233.

14. Adams CE, Jayaram M. Do findings from new trials for schizophrenia fit with existing evidence: not duped...just beguiled? Epidemiol Psichiatr Soc 2007, 16:199-202.

15. Duggan M. Do new prescription drugs pay for themselves? The case of second-generation antipsychotics. J Health Econ 2005, 24:1-31.

16. Montgomery JH, Byerly M, Carmody T, Li B, Miller DR, Varghese F, Holland R. An analysis of the effect of funding source in randomized clinical trials of second generation antipsychotics for the treatment of schizophrenia. Control Clin Trials 2004, 25:598-612.

17. Heres S, Davis J, Maino K, Jetzinger E, Kissling W, Leucht S. Why olanzapine beats risperidone, risperidone beats quetiapine, and quetiapine beats olanzapine: an exploratory analysis of head-to-head comparison studies of second-generation antipsychotics. Am J Psychiatry 2006, 163:185-194.

18. Hotopf M, Churchill R, Lewis G. Pragmatic randomised controlled trials in psychiatry. Br J Psychiatry 1999, 175:217-223.

19. Thornley B, Adams C. Content and quality of 2000 controlled trials in schizophrenia over 50 years. BMJ 1998, 317:1181-1184.

20. Prescott RJ, Counsell CE, Gillespie WJ, Grant AM, Russell IT, Kiauka S, Colthart IR, Ross S, Shepherd SM, Russell D. Factors that limit the quality, number and progress of randomised controlled trials. Health Technol Assess 1999, 3:1-143.

21. Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, Keefe RS, Davis SM, Davis CE, Lebowitz BD, Severe J, Hsiao JK, Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med 2005, 353:1209-1223.

22. McEvoy JP, Lieberman JA, Stroup TS, Davis SM, Meltzer HY, Rosenheck RA, Swartz MS, Perkins DO, Keefe RS, Davis CE, Severe J, Hsiao JK, CATIE Investigators. Effectiveness of clozapine versus olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia who did not respond to prior atypical antipsychotic treatment. Am J Psychiatry 2006, 163:600-610.

23. Jones PB, Barnes TR, Davies L, Dunn G, Lloyd H, Hayhurst KP, Murray RM, Markwick A, Lewis SW. Randomized controlled trial of the effect on Quality of Life of second- vs first-generation antipsychotic drugs in schizophrenia: Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1). Arch Gen Psychiatry 2006, 63:1079-1087.

24. Lewis SW, Barnes TR, Davies L, Murray RM, Dunn G, Hayhurst KP, Markwick A, Lloyd H, Jones PB. Randomized controlled trial of effect of prescription of clozapine versus other second-generation antipsychotic drugs in resistant schizophrenia. Schizophr Bull 2006, 32:715-723.

25. Rosenheck RA, Leslie DL, Sindelar J, Miller EA, Lin H, Stroup TS, McEvoy J, Davis SM, Keefe RS, Swartz M, Perkins DO, Hsiao JK, Lieberman J, CATIE Study Investigators. Cost-effectiveness of second-generation antipsychotics and

perphenazine in a randomized trial of treatment for chronic schizophrenia. Am J Psychiatry 2006 163:2080-2089.

26. Davies LM, Lewis S, Jones PB, Barnes TR, Gaughran F, Hayhurst K, Markwick A, Lloyd H, CUtLASS team. Cost-effectiveness of first- v. second-generation antipsychotic drugs: results from a randomised controlled trial in schizophrenia responding poorly to previous therapy. Br J Psychiatry 2007, 191:14-22.

27. Kahn RS, Fleischhacker WW, Boter H, Davidson M, Vergouwe Y, Keet IP, Gheorghe MD, Rybakowski JK, Galderisi S, Libiger J, Hummer M, Dollfus S, López-Ibor JJ, Hranov LG, Gaebel W, Peuskens J, Lindefors N, Riecher-Rössler A, Grobbee DE, EUFEST study group. Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomised clinical trial. Lancet 2008, 371:1085-1097.

28. Keefe RS, Bilder RM, Davis SM, Harvey PD, Palmer BW, Gold JM. Neurocognitive Working Group. Neurocognitive effects of antipsychotic medications in patients with chronic schizophrenia in the CATIE Trial. Arch Gen Psychiatry 2007, 64:633-47.

29. Davidson M, Galderisi S, Weiser M, Werbeloff N, Fleischhacker WW, Keefe RS. Cognitive Effects of Antipsychotic Drugs in First-Episode Schizophrenia and Schizophreniform Disorder: A Randomized, Open-Label Clinical Trial (EUFEST). Am J Psychiatry 2009, 166:675-82.

30. Ashcroft R. Equipoise, knowledge and ethics in clinical research and practice. Bioethics 1999, 13:314-326.

31. Freedman B. Equipoise and the ethics of clinical research. N Engl J Med 1987, 317:141-145.

32. Loftus EF, Fries JF. Informed consent may be hazardous to health. Science 1979, 204:11.

33. Johnson N, Lilford RJ, Brazier W. At what level of collective equipoise does a clinical trial become ethical? J Med Ethics 1991, 17:30-34.

34. Mills N, Donovon JC, Smith M, Jacoby A, Neal DE, Handy FC. Perceptions of equipoise are crucial to trial participation: a qualitative study of men in the Protect study. Controlled Clin Trials 2003, 24:272-282.

35. Djulbegovic B, Lacevic M, Cantor A, Fields KK, Bennett CL, Adams JR, Kuderer NM, Lyman GH. The uncertainty principle and industry-sponsored research. Lancet 2000, 356:635-638.

36. Gifford R. Community-equipoise and the ethics of randomized clinical trials. Bioethics 1995, 9:127-148.

37. Djulbegovic B. Acknowledgement of uncertainty: a fundamental means to ensure scientific and ethical validity in clinical research. Curr Oncol Rep 2001, 3:389-395.

38. Avins AL: Can unequal be more fair? Ethics, subject allocation, and randomized clinical trials. J Med Ethics 1998, 24:401-408.

39. Chard JA, Lilford RJ. The use of equipoise in clinical trials. Soc Sci Med 1998, 47:891-898.

40. Karlawish JH, Lantos J. Community equipoise and the architecture of clinical research. Camb Q Healthc Ethics 1997, 6:385-396.

41. Alderson P. Equipoise as a means of managing uncertainty: personal, communal and proxy. J Med Ethics 1996, 22:135-139.

42. Elwyn G, Edwards A, Kinnersley P, Grol R. Shared decision making and the concept of equipoise: the competences of involving patients in healthcare choices. Br J Gen Pract 2000, 50:892-899.

43. Chaloner K, Rhame FS. Quantifying and documenting prior beliefs in clinical trials. Stat Med 2001, 20:581-600.

44. Schafer A. The ethics of the randomized clinical trial. N Engl J Med 1982, 307:719-724.

45. Miller FG, Joffe S. Equipoise and the dilemma of randomized clinical trials. N Engl J Med 2011, 364:476-80.

46. Fries JF, Krishnan E. Equipoise, design bias, and randomized controlled trials: the elusive ethics of new drug development. Arthritis Res Ther 2004, 6:250-255.

47. Montori VM, Devereaux PJ, Adhikari NK. Randomized trials stopped early for benefit: a systematic review. JAMA 2005, 294:2203-2209.

48. Bassler D, Briel M, Montori VM. Stopping randomized trials early for benefit and estimation of treatment effects: systematic review and meta-regression analysis. JAMA 2010, 303:1180-1187

49. Wilcox RA, Djulbegovic B, Moffitt HL, Guyatt GH, Montori VM. Randomized trials in oncology stopped early for benefit. J Clin Oncol 2008, 26:18-19

50. Felson DT, Glantz L. A surplus of positive trials: weighing biases and reconsidering equipoise. Arthritis Res Ther 2004, 6:117-119.

51. Schwartz D, Lellouch J. Explanatory and pragmatic attitudes in therapeutical trials. J Chronic Dis 1967, 20:637-648.

52. Weijer C, Shaprio SH, Cranley KC, Enkin MW. Clinical equipoise and not the uncertainty principle is the moral underpinning of the randomised controlled trial. For and against. BMJ 2000, 321:756-758.

53. Sackett DL. Why randomized controlled trials fail but needn't. 1. Failure to gain "coal-face" commitment and to use the uncertainty principle. Can Med Assoc J 2000, 162:1311-1314.

54. Taylor DM, McAskill R. Atypical antipsychotics and weight gain: a systematic review. Acta Psychiatr Scand 2000, 101:416-432.

55. Newcomer JW. Second-generation (atypical) antipsychotics and metabolic effects: a comprehensive literature review. CNS Drugs Suppl 2005, 19:1-93.

56. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. Diabetes 1988, 37:1595-607.

57. Meigs JB, Wilson PWF, Nathan DM D'Agostino RB Sr, Williams K, Haffner SM. Prevalence and characteristics of the metabolic syndrome in the San Antonio heart and Framingham offspring studies. Diabetes 2003, 52:2160-2167.

58. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: Diagnosis and Classification of Diabetes Mellitus, provisional report of a WHO consultation. Diabet Med 1998, 15:539-553,

59. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA 2001, 285:2486-2497.

60. Alberti KG, Zimmet P, Shaw J. Metabolic syndrome--a new world-wide definition. A Consensus Statement from the International Diabetes Federation. Diabet Med 2006, 23:469-80.

61. Malik S, Wong ND, Franklin SS. Impact of the metabolic syndrome on mortality from coronary heart disease, cardiovascular disease, and all causes in United States adults. Circulation 2004, 110:1245-1250.

62. Park Y-W, Zhu S, Palaniappan L. The metabolic syndrome: Prevalence and associated risk factor findings in the US population from the third national health and nutrition examination survey, 1988-1994. Arch Intern Med 2003, 163:427-436.

63. Ilanne-Parikka P, Eriksson JG, Lindstrom J. Prevalence of the metabolic syndrome and its components: Findings from a Finnish general population sample and the diabetes prevention study cohort. Diabetes Care 2004, 27:2135-2140.

64. McEvoy JP, Meyer JM, Goff DC. Prevalence of the metabolic syndrome in patients with schizophrenia: Baseline results from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Schizophrenia Trial and comparison with national estimates from NHANES III. Schizophr Res 2005, 80:19-32.

65. Meyer JM, Nasrallah HA, McEvoy JP. The Clinical Antipsicotic Trials of Intervention Effectiveness (CATIE) Schizophrenia Trial: Clinical Comparison of subgroups with and without the metabolic syndrome. Schizophr Res 2005, 80:9-18.

66. Casey DE, Haupt DW, Newcomer JW, Henderson DC, Sernyak MJ, Davidson M, Lindenmayer JP, Manoukian SV, Banerji MA, Lebovitz HE, Hennekens CH. Antipsychotic-induced weight gain and metabolic abnormalities: implications for increased mortality in patients with schizophrenia, J Clin Psychiatry Suppl 2004, 65:4–18.

67. Mitchell AJ, Malone D. Physical health and schizophrenia. Curr Opin Psychiatry 2006, 19:432–437.

68. Saha S, Chant D, McGrath J. A systematic review of mortality in schizophrenia: is the differential mortality gap worsening over time? Arch Gen Psychiatry 2007, 64:1123–1131.

69. Ray WA, Chung CP, Murray KT, Hall K, Stein CM. Atypical antipsychotic drugs and the risk of sudden cardiac death. N Engl J Med 2009, 360:225-235.

70. Weinmann S, Read J, Aderhold V. Influence of antipsychotics on mortality in schizophrenia: systematic review. Schizophr Res 2009, 113:1-11.

71. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. World Health Organ Tech Rep Ser 2000, 894:1-253.

72. Yusuf S, Hawken S, Ounpuu S. INTERHEART Study Investigators. Obesity and the risk of myocardial infarction in 27,000 participants from 52 countries: a case-control study. Lancet 2005, 366:1640-1649.

73. Schneider HJ, Glaesmer H, Klotsche J, Böhler S, Lehnert H, Zeiher AM, März W, Pittrow D, Stalla GK, Wittchen HU. DETECT Study Group. Accuracy of anthropometric indicators of obesity to predict cardiovascular risk. J Clin Endocrinol Metab 2007, 92:589-594.

74. Sacco RL, Khatri M, Rundek T, Xu Q, Gardener H, Boden-Albala B, Di Tullio MR, Homma S, Elkind MS, Paik MC. Improving global vascular risk prediction with behavioral and anthropometric factors. The multiethnic NOMAS (Northern Manhattan Cohort Study). J Am Coll Cardiol 2009, 54:2303-2311.

75. Steinbrook R, Kassirer JP. Free the data. BMJ 2010, 341:811-812.

76. Leucht S, Kissling W, Davis JM. Second-generation antipsychotics for schizophrenia: can we resolve the conflict? Psychol Med 2009, 39:1591-1602.

77. Stahl SM. Dopamine system stabilizers, aripiprazole, and the next generation of antipsychotics, part 2: illustrating their mechanism of action. J Clin Psychiatry 2001, 62:923-924.

78. Rivas-Vasquez RA. Aripiprazole: A novel antipsychotic with dopamine stabilising properties. Prof Psychol Res Pr 2003, 34:108-111.

79. Food and Drugs Administration (FDA). U.S. Federal Drug Administration CDER. Abilify (aripiprazole) tablets, medical review. http://www.fda.gov/cder/foi/nda/2002/21-436_Abilify.htm. Access verified 9/01/2006.

80. El-Sayeh HG, Morganti C. Aripiprazole for schizophrenia. Cochrane Database Syst Rev 2004:CD004578.

81. OsMed Working Group. [The use of drugs in Italy. National report year 2006] [Italian]. Il Pensiero Scientifico Editore, 2007.

http://www.agenziafarmaco.it/it/content/rapporti-osmed-luso-dei-farmaci-italia. Access verified 22/03/2011.

82. Manschreck TC, Boshes RA. The CATIE schizophrenia trial: results, impact, controversy. Harv Rev Psychiatry 2007, 15:245-258

83. Irving CB, Adams CE, Lawrie S. Haloperidol versus placebo for schizophrenia. Cochrane Database Syst Rev 2006:CD003082.

84. Oosthuizen P, Emsley R, Jadri Turner H, Keyter N. A randomized, controller comparison of the efficacy and tolerability of low and high doses of haloperidol in the treatment of first-episode psychosis. Int J Neuropsychopharmacol 2004, 7:125-131.

85. Leucht C, Kitzmantel M, Kane J, Leucht S, Chua WLLC. Haloperidol versus chlorpromazine for schizophrenia. Cochrane Database Syst Rev 2008:CD004278.

86. El-Sayeh HGG, Morganti C. Aripiprazole for schizophrenia. Cochrane Database of Systematic Reviews 2006:CD004578.

87. Bhattacharjee J, El-Sayeh HGG. Aripiprazole versus typical antipsychotic drugs for schizophrenia. Cochrane Database Syst Rev 2008:CD006617.

88. Komossa K, Rummel-Kluge C, Schmid F, Hunger H, Schwarz S, El-Sayeh HGG, Kissling W, Leucht S. Aripiprazole versus other atypical antipsychotics for schizophrenia. Cochrane Database Syst Rev 2009:CD006569.

89. McQuade RD, Stock E, Marcus R, Jody D, Gharbia NA, Vanveggel S, Archibald D, Carson WH. A comparison of weight change during treatment with olanzapine or aripiprazole: results from a randomized, double-blind study. J Clin Psychiatry Suppl 2004, 18:47

90. Kane JM, Osuntokun O, Kryzhanovskaya LA, Xu W, Stauffer VL, Watson SB. A 28-week, randomized, double-blind study of olanzapine versus aripiprazole in the treatment of schizophrenia. J Clin Psychiatry 2009, 70:572-581.

91. Peto R, Collins R, Gray R. Large-scale randomized evidence: large, simple trials and overviews of trials. Ann N Y Acad Sci 1993, 703:314-340.

92. Tunis SR, Stryer DB, Clancy CM. Practical clinical trials: increasing the value of clinical research for decision making in clinical and health policy. JAMA 2003, 290:1624-1632.

93. Wiener PP. Pragmatism. In: PP Wiener, Editor, *The dictionary of the history of ideas: studies of selected pivotal ideas,* Charles Scribner's Sons, New York, NY (1973) Vol 3, pp. 551–570.

94.. Maclure M. Explaining pragmatic trials to pragmatic policy-makers Can Med Assoc J 2009, 180:1001-1003.

95. March JS, Silva SG, Compton S, Shapiro M, Califf R, Krishnan R. The case for practical clinical trials in psychiatry. Am J Psychiatry 2005, 162:836-846.

96. Platt JR. Strong inference. Science 1964, 146:347–53.

97. Gartlehner G, Hansen RA, Nissman D, Lohr KN, Carey TS. Criteria for Distinguishing Effectiveness From Efficacy Trials in Systematic Reviews. Technical Review 12 (Prepared by the RTI-International-University of North Carolina Evidence-based Practice Center under Contract No. 290-02-0016.) AHRQ Publication No. 06-0046. Rockville, MD: Agency for Healthcare Research and Quality. April 2006.

98. Thorpe KE, Zwarenstein M, Oxman AD, Treweek S, Furberg CD, Altman DG, Tunis S, Bergel E, Harvey I, Magid DJ, Chalkidou K. A pragmatic-explanatory continuum indicator summary (PRECIS): a tool to help trial designers. J Clin Epidemiol 2009, 62:464-475.

99. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar GC. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry Suppl 1998, 20:22-33.

100. Ventura J, Green M, Schaner A. Training and quality assurance with the Brief Psychiatric Rating Scale. The 'drift busters'. Int J Methods Psychiatr Res 1993, 3:221-244.

101. Day JC, Wood G, Dewey M, Bentall RP. A self-rating scale for measuring neuroleptic side-effects. Validation in a group of schizophrenic patients. Br J Psychiatry 1995, 166:650-653.

102. Endicott J, Spitzer RL, Fleiss JL, Cohen J. The global assessment scale. A procedure for measuring overall severity of psychiatric disturbance. Arch Gen Psychiatry 1976, 33:766-771.

103. www.codifa.it. Access verified 12/10/2006.

104. Keck PE, McElroy SL. Bipolar disorder, obesity, and pharmacotherapy-associated weight gain. J Clin Psychiatry 2003, 64:1426-1435.

105. ICH E9 Expert Working Group. Statistical Principles for Clinical Trials. ICH Harmonized Tripartite Guideline. Stat Med 1999, 18:1905-1942.

106. Tyrer P, Kendall T. The spurious advance of antipsychotic drug therapy. Lancet 2009, 373:4-5.

107. Neuhäuser M. How to deal with multiple endpoints in clinical trials. Fundam Clin Pharmacol 2006, 20:515-523.

108. Essock SM, Covell NH, Davis SM, Stroup TS, Rosenheck RA, Lieberman JA. Effectiveness of switching antipsychotic medications. Am J Psychiatry 2006, 163:2090-2095.

109. Rosenheck RA, Davis S, Covell N, Essock S, Swartz M, Stroup S, McEvoy J, Lieberman J. Does switching to a new antipsychotic improve outcomes? Data from the CATIE Trial. Schizophr Res 2009, 107:22-29.

110. http://ricerca-clinica.agenziafarmaco.it/it/node/index.php?RICERCA_LIBERA=gisas&OPERAZIONE=AND&q=node%2F331&Cerca=yes&PAGE=1. Access verified 18/05/2011.

111. http://clinicaltrials.gov/ct2/results?term=gisas. Access verified 18/05/2011.

112. Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. Lancet 2001, 357:1191-1194.

113. Campbell MK, Snowdon C, Francis D. Recruitment to randomised trials: strategies for trial enrollment and participation study. The STEPS study. Health Technol Assess 2007, 11(48).

114. Ross S, Grant A, Counsell C. Barriers to participation in randomised controlled trials: a systematic review. J Clin Epidemiol 1999, 52:1143-1156.

115. Fayter D, McDaid C, Eastwood A. A systematic review highlights threats to validity in studies of barriers to cancer trial participation. J Clin Epidemiol 2007, 60:990-1001.

116. Mc Daid C, Hodges Z, Fayter D. Increasing participation of cancer patients in randomised controlled trials: a systematic review. Trials 2006, 7:16.

117. Josefson D. Marketing of antipsychotic drugs attacked. BMJ 1998, 316:648.

118. Angell M. Is academic medicine for sale? N Engl J Med 2000, 342:1516-1518.

119. Arbuckle MR, Gameroff MJ, Marcus SC. Psychiatric opinion and antipsychotic selection in the management of schizophrenia. Psychiatr Serv 2008, 59:561-565.

120. Sackett DL. Equipoise, a term whose time (if it ever came) has surely gone. CMAJ 2000, 163:835-836.

121. Sackett DL. Bias in analytic research. J Chronic Dis 1979, 32:51-63.

122. Lloyd HM, Markwick AJ, Page ER. Attitudes to atypical and conventional antipsychotic drug treatment in clinicians participating in the CUtLASS study. Int J Psychiatry Clin Pract 2005, 9:35-40.

123. Spaar A, Frey M, Turk A. Recruitment barriers in a randomized controlled trial from the physicians' perspective: a postal survey. BMC Med Res Methodol 2009, 9:14.

124. OsMed Working Group. [The use of drugs in Italy. National report year 2008] [Italian]. Il Pensiero Scientifico Editore, 2009. http://www.agenziafarmaco.it/it/content/rapporti-osmed-luso-dei-farmaci-italia. Access verified 22/03/2011.

125. Walker MC, Li LM, Sander JW. Long-term use of lamotrigine and vigabatrin in severe refractory epilepsy: audit of outcome. BMJ 1996, 313:1184–1185.

126. Anderson IM. Selective serotonin reuptake inhibitors versus tricyclic antidepressants: a meta-analysis of efficacy and tolerability. J Affect Disord 2000; 58:19–36.

127. Essock SM, Schooler NR, Stroup TS, McEvoy JP, Rojas I, Jackson C, Covell NH; The Schizophrenia Trials Network. Effectiveness of Switching From Antipsychotic Polypharmacy to Monotherapy. Am J Psychiatry 2011 May 2. [Epub ahead of print]

128. Liu-Seifert H, Adams DH, Kinon BJ. Discontinuation of treatment of schizophrenic patients is driven by poor symptom response: a pooled post-hoc analysis of four atypical antipsychotic drugs. BMC Med 2005, 3:21.

129. Kinon BJ, Liu-Seifert H, Adams DH, Citrome L. Differential rates of treatment discontinuation in clinical trials as a measure of treatment effectiveness for olanzapine and comparator atypical antipsychotics for schizophrenia. J Clin Psychopharmacol, 26:632-637.

130. Dunayevich E, Ascher-Svanum H, Zhao F, Jacobson JG, Phillips GA, Dellva MA, Green AI. Longer time to antipsychotic treatment discontinuation for any cause is associated with better functional outcomes for patients with schizophrenia, schizophreniform disorder, or schizoaffective disorder. J Clin Psychiatry 2007, 68:1163-1171.

131. Olfson M, Marcus SC, Tedeschi M, Wan GJ. Continuity of antidepressant treatment for adults with depression in the United States. Am J Psychiatry 2006, 163:101-108.

132. Sajatovic M, Valenstein M, Blow F, Ganoczy D, Ignacio R. Treatment adherence with lithium and anticonvulsant medications among patients with bipolar disorder. Psychiatr Serv 2007, 58:855-863.

133. Rosholm JU, Andersen M, Gram LF. Are there differences in the use of selective serotonin reuptake inhibitors and tricyclic antidepressants? a prescription database study. Eur J Clin Pharmacol 2001, 56:923–929.

134. Anderson IM, Tomenson BM. Treatment discontinuation rates with selective serotonin reuptake inhibitors compared with tricyclic antidepressants: a meta-analysis. BMJ 1995, 310:1433–1438.

135. Hotopf M, Hardy R, Lewis G. Discontinuation rates of SSRIs and tricyclic antidepressants: a meta-analysis and investigation of heterogeneity. Br J Psychiatry 1997, 170:120–127.

136. Tai-Seale M, Croghan TW, Obenchain R. Determinants of antidepressant treatment compliance: implications for policy. Med Care Res Rev 2000, 57:491–512.

137. Fairman K, Drevets W, Kreisman J, Teitelbaum FF. Course of antidepressant treatment, drug type, and prescriber's specialty. Psychiatr Serv 1998, 49:1180–1186.

138. Simon G, VonKorff M, Wagner EH, Barlow W. Patterns of antidepressant use in community practice. Gen Hosp Psychiatry 1993; 15:399–408

139. Lawrenson RA, Tyrer F, Newson RB, Farmer RDT. The treatment of depression in UK general practice: selective serotonin inhibitors and tricyclic antidepressants compared. J Affect Disord 2000, 59:149–157

140. Tournier M, Moride Y, Crott R, du Fort GG, Ducruet T. Economic impact of non-persistence to antidepressant therapy in the Quebec community-dwelling elderly population. J Affect Disord 2009, 115:160-166.

141. Siiskonen SJ, Breekveldt-Postma NS, Vincze G, Khan ZM, Erkens JA, Herings RM. Higher persistence with valsartan compared with enalapril in daily practice. Vasc Health Risk Manag 2007, 3:1039-1044.

142. Kreyenbuhl J, Slade EP, Medoff DR, Brown CH, Ehrenreich B, Afful J, Dixon LB. Time to discontinuation of first- and second-generation antipsychotic medications in the treatment of schizophrenia. Schizophr Res 2011, 131:127-132.

143. Vlahiotis A, Devine ST, Eichholz J, Kautzner A. Discontinuation rates and health care costs in adult patients starting generic versus brand SSRI or SNRI antidepressants in commercial health plans. J Manag Care Pharm 2011, 17:123-32.

144. Eyding D, Lelgemann M, Grouven U, Härter M, Kromp M, Kaiser T. Reboxetine for acute treatment of major depression: systematic review and meta-analysis of published and unpublished placebo and selective serotonin reuptake inhibitor controlled trials. BMJ 2010, 341:c4737.

145. Barbato A, Parabiaghi A, Panicali F, Battino N, D'Avanzo B, de Girolamo G, Rucci P, Santone G; on behalf of the Progres-Acute Group. Do patients improve after short psychiatric admission? A cohort study in Italy. Nord J Psychiatry 2010, 65:251-258.

146. D'Agostino RB, Wolf PA, Belanger AJ, Kannel WB. Stroke risk profile: adjustment for antihypertensive medication: The Framingham Study. Stroke 1994, 25:40–43.

147. Wilson W, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation 1998, 97:1837–1847.

148. Global Vascular Risk Score Calculator. http://neurology.med.miami.edu/gvr/gvr.htm. Access verified 22/03/2011.

149. Rubin DB. Inference and Missing Data. Biometrika 1976, 63:581-592.

150. Parabiaghi A, Rapisarda F, D'Avanzo B, Erlicher A, Lora A, Barbato A. Measuring clinical change in routine mental health care: differences between first time and longer term service users. Aust N Z J Psychiatry 2011, 45:558-568.

151. Perkins DO, Gu H, Weiden PJ, McEvoy JP, Hamer RM, Lieberman JA. Comparison of Atypicals in First Episode study group. Predictors of treatment discontinuation and medication nonadherence in patients recovering from a first episode of schizophrenia, schizophreniform disorder, or schizoaffective disorder: a randomized, double-blind, flexible dose, multicenter study. J Clin Psychiatry 2008, 69:106-113.

152. McEvoy JP, Lieberman JA, Perkins DO, Hamer RM, Gu H, Lazarus A, Sweitzer D, Olexy C, Weiden P, Strakowski SD. Efficacy and tolerability of olanzapine, quetiapine, and risperidone in the treatment of early psychosis: a randomized, double-blind 52-week comparison. Am J Psychiatry 2007, 164:1050-1060.

153. Abraha I, Montedori A. Modified intention to treat reporting in randomised controlled trials: systematic review. BMJ 2010, 340:c2697.

154. Beyer-Westendorf J, Büller H. External and internal validity of open label or double-blind trials in oral anticoagulation: better, worse or just different? J Thromb Haemost. 2011, 9:2153-2158.

APPENDIX 1

GSAS

MANUAL OF PROCEDURES

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1. REQUISITES AND TASKS OF EACH SITE TAKING PART

The 'Mario Negri' Institute for Pharmacological Research is the sole and independent sponsor of this study. Scientific co-ordination of the study will be managed entirely by the Institute's *Unit of Epidemiology and Social Psychiatry*.

Each site taking part in the study must be found suitable for taking part in pharmacological clinical studies. It must therefore be a healthcare facility belonging to a Local Health Unit or Hospital, to a University, to a public or private "IRCSS" (scientific institute for in-patient and out-patient care) or to a privately owned centre recognised by and linked by special arrangements to the Italian National Health Service (SSN). It must be considered suitable by the Health Ministry for holding clinical trials with drugs, in accordance with the provisions contained in Ministry Decree dated 19th March 1998.

Each **site taking part** must be a specialised clinical centre operating in the field of mental health and dealing with the treatment of patients with schizophrenia.

A **recruitment centre** is defined as the functional unit of the participating site, at which it is expected to **recruit at least 10 patients.**

Each participating site may have more than one recruitment centre at its disposal, depending on the agreements reached with Istituto 'Mario Negri'. A code **(recruitment centre code)** will be assigned to each recruitment centre.

Patient recruitment at each centre is planned to last for one year, after which each patient must be followed up for one year. The study will therefore last for approximately two years.

The psychiatrist appointed as Principal Investigator is **responsible for performing the activities that, according to the protocol and to this Manual, are to be carried out** by the recruitment centre. He/she may delegate the various activities to other personnel of the service, subject to prior notification of the Scientific Secretariat.

Each patient included in the study must have a **treating psychiatrist,** who will be responsible for the treatment assigned to him/her.

The Principal Investigator must monitor progress of the trial for its whole duration. To this end, he/she must create an **Excluded Patients Register**, make sure that a **Study Chart** is completed for each patient and complete the **CONSORT chart**. It is important that, if these three tasks are delegated to someone else, they should all be entrusted to the same person.

The group of GiSAS investigators consists of:

- **The Principal Investigators** and the persons delegated by them;
- **the treating psychiatrists or recruiting psychiatrists**;
- **other personnel at the sites taking part.**

Those patients who are enrolled in the study must be taken into care in accordance with the participating site's usual practice.

The following forms will have to be completed:

(a) **Recruitment Forms** (at the time of recruitment);

(b) **Randomization Forms** (at the time of randomization);

(c) **Baseline Forms** (after randomization);

(d) **Treatment Forms** (whenever the treatment assigned is altered and in any case at least once a month);

(e) **Treatment and Follow-Up Forms** (upon discontinuing treatment);

(f) **Treatment and Follow-Up Forms** (at month 12, also for those who have already stopped taking the drug).

GiSAS Investigators must follow their patients and monitor the pharmacological treatment throughout the duration of the study. They are responsible for carrying out all the tests envisaged, for scheduling the assessments and for completing the scales and forms.

The study calls for **some blood samples to be taken** from the subjects recruited (see Study Protocol). These samples will be **analysed centrally** by Istituto 'Mario Negri'. It is, however, necessary for them to be prepared and stored by the recruitment centres in order for a certain number of samples to be accumulated before they are collected by Istituto 'Mario Negri'.

Each recruitment centre must therefore have a reference laboratory and must take care of ensuring that the blood samples reach it.

Each reference laboratory must, in turn, take care of centrifuging, freezing and storing the samples at -30/-70°C. Subsequent transport of the samples to the centralised laboratory and testing of all the samples will be taken care of by Istituto 'Mario Negri'.

The instructions for taking the samples and for preparing them are attached to this manual (**Attachment 1**).

The clinical trial drugs must be prescribed by the clinicians in accordance with the habitual procedures used at the participating sites and with the rules of Good Clinical Practice, observing in particular the contraindications, the special warnings and the precautions associated with use indicated on the technical data sheets of the drugs contained in the Investigator's Brochure.

Flexible dosages adapted to the needs of each single patient must be used, within the framework of the following doses based on the international guidelines: aripiprazole 10-30 mg/day, olanzapine 10-20 mg/day, haloperidol 3-10 mg/day. Based on the contents of sub-section 1 of Article 2 of the Ministry Decree dated

17th December 2004, since these drugs are being used for indications specified in the authorisation to place them on the market, **they are for account of the Italian National Health Service.**

It is recalled here that patients for whom even only one of the clinical trial drugs is specifically contraindicated **cannot be included in the study.**

2. PATIENT RECRUITMENT

SCREENING

All **patients of age** being followed by the service with a **diagnosis of schizophrenia** can access this stage, and will therefore be evaluated for eligibility to take part in the study.

It is important to take into account also patients whose current diagnosis is not schizophrenia. Thus, it is advisable to evaluate the eligibility also of patients who do not appear to be schizophrenic but who are in any case receiving antipsychotic treatment, as systematic use of **Module M of the MINI** can contribute towards a revision of some diagnoses and is in any case useful for achieving greater uniformity of diagnosis among the participating sites.

Starting from the date on which recruitment begins, the **recruiting psychiatrist** must screen his/her patients, completing a **Recruitment Form** for each potentially eligible subject. To do this, in the last week of each month (**GiSAS week**) he/she shall evaluate systematically the eligibility of all the patients he/she sees.

The Recruitment Form of each patient admitted to the trial must be initialled and marked with the patient code to be assigned at the time of *automatic randomization*. It shall then be kept in a special **blue folder for each patient**, known as the **GiSAS Folder or Case Report Form (CRF)**.

The Recruitment Forms of the excluded patients (to whom no patient code has been assigned) must, on the other hand, be kept in a **green folder,** called the **Excluded Patients Register**.

During the recruitment stage, each treating psychiatrist shall create his/her own Excluded Patients Register. During the **GiSAS week,** eligibility of all the previously excluded patients shall be re-assessed, taking into account the fact that **some eligibility criteria may change during the course of the recruitment year.**

INCLUSION AND EXCLUSION CRITERIA

The assessment of eligibility of patients to take part in the study calls for **three levels.**

1 - Preliminary assessments by the Investigator:

- check of the diagnosis (**MINI, module M**);
- absence of type II diabetes and of metabolic syndrome: patients must be screened for any such conditions by their treating psychiatrists;
- absence of contraindications for the treatment assigned;
- evaluation of the patient's willingness, informed consent.

Each patient admitted to **randomization** will be assigned a number (patient code) and go on to the **TRIAL STAGE.**

2 - Clinical investigation and blood sampling for centralised testing:

N.B. These must be carried out **BEFORE** the clinical trial drug is taken.

3 - Assessment by Istituto 'Mario Negri':

- Check of the absence of diabetes and or metabolic syndrome, based on an assessment of the results of the centralised laboratory tests.

If a patient who was initially assessed as negative with regard to the criteria of **metabolic syndrome or of diabetes** were to be found positive on the basis of the **results of the centralised tests**, this would be sufficient **reason for his/her exclusion from the study**. Such a patient would, therefore, have to be excluded and replaced with another. Istituto 'Mario Negri' undertakes to notify the results as soon as the data concerning the tests are available.

INFORMED CONSENT

Informed consent is the procedure by means of which a subject agrees voluntarily to take part in a clinical study. **It is the duty of the treating psychiatrist to obtain the subject's informed consent.**

Sufficient time must be devoted to the process of informing the patient, which must be done in a suitable place and using suitable language. The **Patient Information Sheet** provided by Istituto "Mario Negri" is in addition to and does not replace the doctor-patient interview. The **time of providing the information must be officially recorded in the patient's clinical records.**

The rules of *Good Clinical Practice* (Ministry Decree dated 15th July 1997) state that a subject taking part in a clinical trial **must give his/her written consent beforehand, and that such consent may be withdrawn at any time.** Said written informed consent is provided as a special form that has to be signed and dated personally by the subject and by the treating psychiatrist in two copies.

One copy will be handed over to the patient while the other will be kept in his/her GiSAS Folder.

In the event of hospitalisation, a copy of the informed consent form must be attached to the patient's clinical records.

If a patient is of unsound mind, his/her tutor will sign the informed consent form. If said unsound condition is of a temporary nature, the consent form can be signed on an interim basis by the patient's closest relative and, at a later time, by the patient him/herself.

CONSORT DIAGRAM

A CONSORT diagram is a flow chart describing progress of the subjects through the various stages of a clinical study.

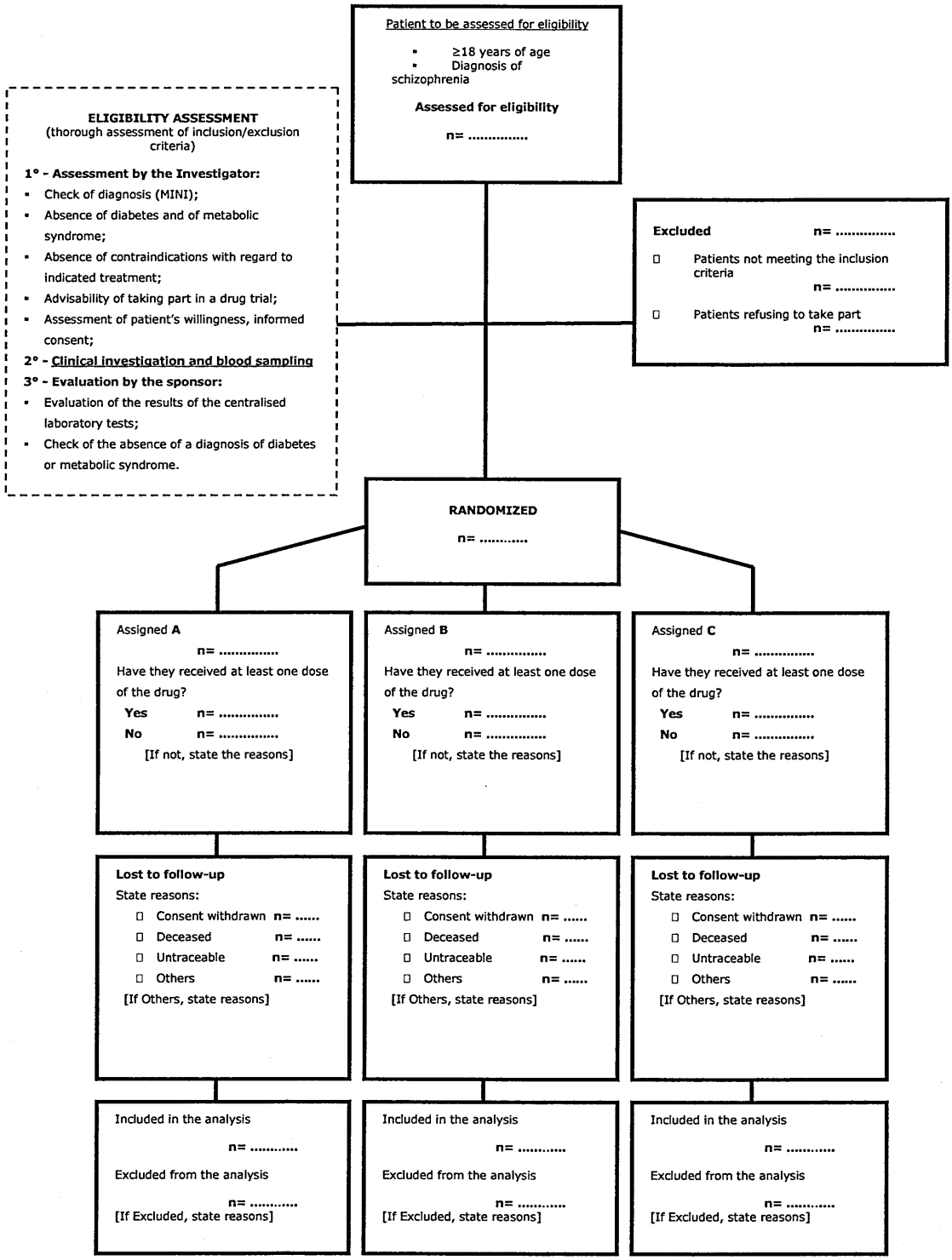
It is up to the Principal Investigator to complete the CONSORT Diagram. A single diagram must be prepared for each site taking part, and will be collected at the end of the study.

The diagram will therefore take all the subjects assessed during the screening stage and all the subjects recruited at that site into account.

The information used to prepare the diagram will be based on the **Recruitment Forms** completed for all eligible patients.

The Recruitment Forms of the patients included in the trial must be initialled and marked with the patient code and kept in special **blue folders** known as the **GiSAS Folders**. The Recruitment Forms of the excluded patients (with no patient codes) must, on the other hand, be kept in a **green folder** called the **Excluded Patients Register**.

Figure 2. CONSORT Diagram



3. CONDUCTING THE TRIAL

A **Baseline Form** must be completed at the earliest opportunity for all patients included in the trial and randomised. As soon as this has been done, the patient may start to take the drug assigned to him/her.

During the 12 months for which the study will last, the antipsychotic therapy and any concomitant therapy must be carefully monitored. This monitoring will be certified by completing a **Treatment Form**, which must be done **at least once a month and whenever the antipsychotic therapy is altered** (each Treatment Form must be sent to Istituto 'Mario Negri' by telefax).

If the treatment is DISCONTINUED, another **Treatment Form** must be completed, taking care to indicate clearly the **date on which it was discontinued and the reason** (Drug Discontinuation Form). This completed form must then be sent in by fax and the **follow-up** medical examination and blood sampling scheduled. It is important that **not more than 3 weeks should pass** between the time of discontinuing the treatment and the follow-up assessment.

Follow-up assessments must be carried out if and when **treatment is discontinued,** and at the deadline of **12 months from the date of randomization**. In both cases, both the Treatment Form and the Follow-up Form must be completed.

STUDY CHART

This chart must be filed in by the treating psychiatrist. The Principal Investigator must check that it has been completed.

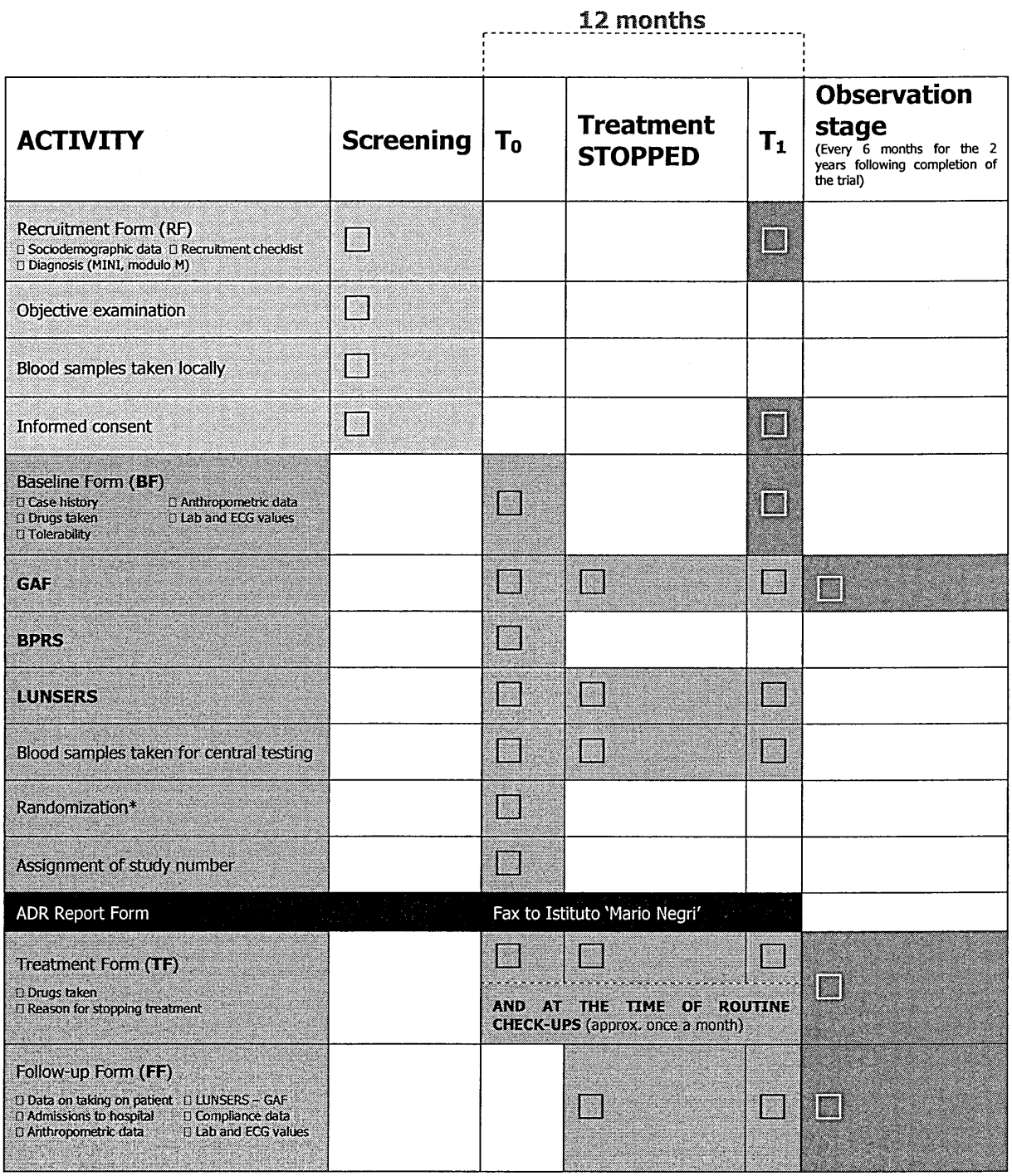
SCREENING PHASE: The yellow part, concerning selection of the patients, has to be completed at the time of inclusion.

TRIAL PHASE: the single items of the part concerning the actual trial (in green in the diagram) must be filled in after each activity has been completed.

OBSERVATION PHASE: All those patients who have completed month 12 follow-up assessment will be candidates for the observation stage. It is planned to assess the patients included in this stage every six months for the following two years, completing the Treatment Form and the Follow-up Form.

This stage will constitute a separate study, the protocol for which will be notified to the Ethics Committees of the participating sites. It is therefore planned to include only those patients who give their specific informed consent.

Figure 1. Study Diagram



RANDOMIZATION

Randomization is an automatic procedure and the service is therefore active **every day, 24 hours a day, phone number +390239014915.**

A recorded voice asks the necessary questions for: (a) **identifying the recruitment centre**; (b) **checking the inclusion and exclusion criteria.**

The Investigator must follow the instructions, replying by pressing the appropriate numerical keys. If the key corresponding to the expected answer is not pressed, the randomization procedure will be broken off. If this occurs simply due to a mistake in making the entries, it is necessary to ring off and start the procedure from the beginning again.

The randomization date will be considered as the **date of starting the study**. If it is not possible to **administer the drug assigned to the patient** on the same day, it must be administered as soon as possible and in any case **within 7 days.**

The fact that the randomised patient has taken **at least one dose of the drug,** which is the **criterion for actual inclusion in the study**, must be **confirmed by the Investigator** by faxing the Randomization Form to Istituto 'Mario Negri'.

This means that the Randomization Form should not be sent in before the patient has actually started taking the treatment.

If the patient has not yet taken the drug assigned to him/her within the seven-day deadline, please contact immediately Istituto 'Mario Negri'.

DRUG SWITCHES

Attached to the Manual are drug switching guidelines, for the purpose of providing tips for replacing antipsychotic treatment being taken at the time of recruitment with that assigned by the randomization procedure (**Attachment 2**).

The switch must be achieved **within one month from the time of taking the first dose of the drug**.

DISCONTINUATION OF TREATMENT

The assigned antipsychotic treatment will be said to have been discontinued:

(a) when the patient and/or the treating psychiatrist decide to stop using the assigned drug;

Or

(b) when another antipsychotic drug is added to the one assigned.

Cases of ***temporary and occasional discontinuation*** (so-called *drug holidays*) **are exceptions** to point (a). This means that it is possible for the patient to stop taking the treatment provided (1) this does not happen more than once over a period of six months and that (2) the *holiday* lasts less than two weeks.

If, for example, it is found that a patient has stopped taking the drug assigned to him/her for a week, this does not entail the obligation to report that the treatment has been discontinued, unless the patient has already stopped taking the drug on at least one other occasion in the previous six months. If he/she stops taking the drug for two weeks or more, on the other hand, it will be compulsory to report that the treatment was discontinued.

An exception to point (b) is **occasional parenteral antipsychotic treatment**. In this latter case, no operational definition of the term *occasional* is provided since non-depot intramuscular antipsychotic treatment is usually administered in emergency situations.

After stopping the treatment, it may happen that the patient starts taking the drug assigned by the randomization procedure again, either on its own or associated with another antipsychotic drug.

In any case, once the assigned drug has been discontinued, it is no longer necessary to monitor the drug treatment (Treatment Form).

For patients who stop taking the treatment and therefore are no longer being monitored, the information on the drugs taken up to the time of the one-year follow-up must in any case be acquired, completing on that occasion only the Treatment Form.

MEDICAL CHECK-UP AND TESTS

The treating psychiatrist has the task of carrying out a **medical check-up,** at which time the following parameters must be measured: height, weight, blood pressure, abdominal circumference and hips.

The treating psychiatrist also has the task of scheduling the **blood chemistry and instrumental tests for account of the service (haemochrome and ECG)** and of arranging for the blood samples to be sent to the reference laboratory for **centrifuging and freezing**.

The check-up, the tests and the sampling are carried out:

(a) after inclusion in the study

baseline, t_0

(b) upon stopping the treatment assigned

Follow-up 1, t_1

(c) in month 12 from randomization

Follow-up 2, t_2

ABDOMINAL CIRCUMFERENCE

The abdominal circumference, also known as waist circumference, is an indirect measurement of intra-abdominal visceral fat. It has to be measured and rounded off to the first decimal place (0.1 cm).

Istituto 'Mario Negri' will provide special measuring tapes made of flexible and undeformable material.

Each measuring tape is connected to a spring-operated device that will allow it to be tightened around the abdomen with a force of 750 grams.

The waist must be measured at its narrowest point, in the area between the superior iliac spine and the lower margin of the rib cage (usually at the height of the navel). With the patient standing up straight, the measuring tape must be applied to the bare skin, holding it parallel to the ground. While the measurement is being carried out, the patient must be relaxed and must breathe freely, with his/her arms hanging loosely at his/her sides.

HIP CIRCUMFERENCE

The hip circumference must be measured and rounded off to the first decimal place (0.1 cm). The same measuring tapes used to measure the abdominal circumference will be used. Each measuring tape is connected to a spring-operated device enabling it to be tightened around the hips with a force of 750 grams.

The circumference must be measured around the buttocks, at the height of the femoral head, in the place where the hips are at their widest.

With the patient standing upright, the tape must be placed over his/her underwear and held parallel to the ground.

WAIST-TO-HIP RATIO

This is the ratio of the abdominal circumference to that of the hips.

ECG

The ECG must be **carried out by the participating sites**. Copies of the electrocardiogram and report must be attached to the CRF and the information contained in the report must be copied onto the CRF by the treating psychiatrist.

SAMPLING PROCEDURE

The treating psychiatrist must arrange for the samples to be taken according to the standard procedures and to send them to the reference laboratory, where they will be **centrifuged and frozen at a temperature between -30 and -70°C.** Istituto 'Mario Negri' will make arrangements with the reference laboratory for collecting the samples and sending them to the centralised laboratory. Instructions for taking and collecting the blood samples are attached to this manual (**Attachment 1**).

HAEMOCHROME

Haemochromocytometric testing and testing of the leukocyte formula and electrolytes must be **carried out by the participating site**. Copies of the reports must be attached to the CRF and the results be copied onto the CRF by the Investigator.

OTHER TESTS

Patients who, at the time of their follow-up tests, have **fasting blood-sugar values exceeding 126 mg/dl** must be tested by their participating site in order to exclude or confirm the diagnosis of diabetes.

Istituto 'Mario Negri' undertakes to notify the codes of those patients who have high blood-sugar values as soon as the results of the tests are available.

Patients who are reported as above will have to repeat the test for assessing their **fasting blood-sugar levels** and must undergo **testing for their glycaemic loads**.

These tests must be carried out by the participating site and are for the latter's account, since they are part of a routine in-depth diagnostic procedure indicated specifically in standard guidelines.

The treating psychiatrists undertake to inform Istituto 'Mario Negri' of the results of the tests, attaching copies of the results to the patient's Follow-up Form.

ASSESSMENT SCALES

MINI

The *Mini International Neuropsychiatric Interview*[1] (MINI) is a short structured interview enabling formulation of 14 **Axis I diagnoses according to the criteria of DSM IV**, formulation of an Axis II diagnosis (Antisocial Personality Disorder) and evaluation of the risk of suicide. The authors referred to the CIDI (*Composite International Diagnostic Interview*), trying to simplify the diagnostic procedures for easier and faster use in clinical practice.

This tool has a modular structure, each module corresponding to a diagnostic area. Each area includes one or two preliminary questions requiring dichotomous answers (YES/NO). A reply in the negative to these questions indicates the absence of the related diagnosis and the need to go on to the next module. A reply in the affirmative, on the other hand, implies the possible presence of the diagnosis being investigated and therefore the need to go into the criteria to be met in further depth.

The period of time to be assessed is specified for each diagnosis and may span from the length of the interview to the interviewee's whole life, depending on what is specifically required for each diagnosis.

In this study, reference is made solely to module M of the MINI, which concerns the schizophrenia diagnostic area.

BPRS

The *Brief Psychiatric Rating Scale*[2] (BPRS) is a **multi-factor psychopathological rating scale** developed with the intention of providing a minimum set of phenomenological characteristics capable of characterising the psychopathological state of the patient.

In the GiSAS study, the version extended to 24 items is used, together with the related instruction manual (BPRS 4.0)[3]. The manual is a sort of semi-structured interview providing detailed instructions on how to detect the presence of the symptoms and on assessing how serious they are. Each item refers to a specific symptom. The score for

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1 **Sheehan DV, Lecrubier Y et al.** MINI International Neuropsychiatric Interview (M.I.N.I.). University of South Florida Institute for Research in Psychiatry,
Tampa, Florida and INSERM – Hôpital de la Salpêtrière, Paris, France, 1994.

2 **Lukoff D,, Nuechterlein K & Ventura J.** Manual for the expanded Brief Psychiatric Rating Scale. Schizophrenia Bulletin 12:594-602, 1986.

3 **Ventura J,, Green MF, ,Shaner A & Liberman RP.** Training and quality assurance with the Brief Psychiatric Rating Scale: "The drift busters". International Journal of Methods in Psychiatry Research 3:221-6, 1993

each item is assigned by means of a 7-point Likert–type scale (1 = absent to 7 = very serious).
In assigning the score, the treating psychiatrist must keep a hierarchical criterion in mind, referring to the highest level of seriousness of the symptoms in the period of time considered and must consider the aspect for which the prejudice appears to be at its greatest (frequency or gravity). The reference period of time is the month preceding the interview.

For each symptom the manual indicates an operational definition of the various levels of seriousness (anchor points): a score of 1 refers to a sub-clinical situation, a score of 2 to 3 to a mild symptom, a score of 4 to 5 to a moderate symptom and a score of 6 to 7 to a serious symptom. It is necessary, initially, to *anchor* oneself to one of these levels of seriousness and, only subsequently, to choose an intermediate score (e.g. 4 or 5).
The symptoms must be identified and their seriousness be defined through the clinical interview, direct observation and the use of other sources (e. family members and friends, other staff members, clinical records).
The manual specifies which sources should be used to complete each item (see Table 1).
In the GiSAS study, the **BPRS** is used to evaluate how **serious the patients are at the baseline.** The scale must therefore be applied to the patients only at the time of their inclusion. The overall score, consisting of the sum of the scores for the 24 items has to be entered on the Recruitment Form.

Table 1. Reference sources for the BPRS

BPRS 4.0

1. Somatic concern	13. Self-neglect
2. Anxiety	14. Disorientation
3. Depression	15. Conceptual disorganisation
4. Suicidality	16. Blunted affect
5. Guilt	17. Emotional withdrawal
6. Hostility	18. Motor retardation
7. Elated mood	19. Tension
8. Grandiosity	20. Uncooperativeness
9. Suspiciousness	21. Excitement
10. Hallucinations	22. Distractibility
11. Unusual thought content	23. Motor hyperactivity
12. Bizarre behaviour	24. Mannerisms and posturing

☐ Items 1-6, 8-11: Take the patient's own statements (clinical interview) or what he has said to others (other sources) into account.

▒ Items 7+12+13: ALSO take the behaviour observed (direct observation + clinical interview / other sources) into account

■ Items 15-24: Take ONLY observed behaviour or the type of language used into account (direct observation).

GAF

The *Global Assessment of Functioning scale*[4] (GAF) is an **assessment scale of the global type**. It was developed in order to assess the overall seriousness of a patient on the basis of a pre-defined scale, regardless of the psychopathological complexity and of the nature of the psychiatric disorder. It was originally included in DSM-III-R and in **DSM-IV as Axis V** of the multi-axis classification.

The period of time that the treating psychiatrist has to consider is the month preceding the interview. The assessment of the seriousness refers both to the psychopathological aspects and to psychosocial and job-related functioning in a hypothetical continuum calling for assignment of a score of 100 for a situation of full mental health or ideal functioning and a score of 1 to a dysfunction serious enough to prejudice the very survival of the person.

The numerical scale is split up into 10 anchor points, each of which defines a level of seriousness. For each level, a reference description is provided which should match the patient's situation. Each anchor point is in turn further divided up into 10 points.

4 **DSM-IV** (1995) Washington DC: A.P.A. Press.

The range from **81 to 100** refers to conditions of absence of mental disease and good functioning, characterised by the presence of positive features (richness of interests and social relations, warmth, positive attitude towards life). The range from **71 to 80** indicates a marginal presence of mental illness or difficulty of functioning, and the range from **1 to 70** indicates the presence of mental disease or problems in functioning of different degrees of seriousness. Within this range, the cut-off level of 50 should be kept in mind. Scores below this level (**≤50**) refer to situations varying from moderately to extremely serious (Severely Mentally Ill, SMI).

Lastly, in assigning the score, the psychiatrist must keep a hierarchical criterion in mind, referring to the lowest level of functioning reached by the patient in the period of time considered (approximately one month) and considering the score in the area which appears to be most severely prejudiced (symptoms or social functioning).

In the GiSAS study, the GAF is used to assess the overall effectiveness of the drug assigned to the patient. The score must be entered on the CRF both at the baseline and at the time of the follow-up.

LUNSERS

The *Liverpool University Neuroleptic Side-Effect Rating Scale*[5] (LUNSERS) is a 51-item **self-rating scale** to be used by the patient, indicating the conditions affecting him/her and their intensity. The patient must be asked explicitly to indicate the symptoms that he/she feels are side effects of the antipsychotic treatment he/she is taking. Those patients who at the time of recruitment have not been taking any antipsychotic treatment for over one month and who do not exhibit any residual side effects (e.g. obesity, tardive dyskinesia) need not complete the LUNSERS. In these cases the treating psychiatrist shall indicate the reason for not doing so on the Recruitment Form in the area next to that provided for indicating the LUNSERS score.

The score for each symptom is assigned using a 5-point Likert-type scale (1= not at all to 5 = very much). The reference period of time is the month preceding the interview.

The questionnaire contains 41 questions referring to specific and proven side effects of neuroleptic drugs.

The remaining 10 questions, scattered at random throughout the list, are, on the other hand, *"red herring"* items having the purpose of drawing attention to unreliable side

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5 ***Day JC, Wood G, Dewey M, Bentall RP.** A self-rating scale for measuring neuroleptic side-effects. Validation in a group of schizophrenic patients. *British Journal of Psychiatry* 166:650-3, 1995.

effects. That is to say, these symptoms, such as hair loss and chilblains, have nothing to do with the effects of the antipsychotic drugs and might be indicated by patients who tend to overestimate the negative effects of the drugs.
In the intentions of the authors, the total score of the "red herring" items (numbers 3, 8, 11, 12, 25, 28, 30, 33, 42 and 45) would identify those subjects who tend to give imprecise answers, thus providing an index of the reliability of the results.
The psychiatrist is required simply to calculate the overall score, consisting of the sum of all fifty-one answers, to be entered on the CRF, both at the baseline and at the time of the follow-up. The score referred to the "red herring" and the difference between the two scores, on the other hand, will be calculated by Istituto 'Mario Negri'.

USING THE ASSESSMENT SCALES

Use of the assessment scales and the manner in which they are to be completed are summarised in Table 3.

Table 3. Using the assessment scales

Which?	*Why?*	*When?*	*Where?*
MINI	To confirm or formulate the diagnosis of schizophrenia	Screening	Recruitment Form
BPRS	To assess the severity of the symptoms	Baseline	Baseline Form
GAF	To assess the overall severity and psychosocial functioning	Baseline and Follow-up	Baseline Form and Follow-up Form
LUNSERS	To assess the side effects from the patient's point of view	Baseline and Follow-up	Baseline Form and Follow-up Form

ASSESSMENT FORMS

GENERAL PROCEDURE FOR COMPLETING THE FORMS

All the forms for acquiring data for the study are supplied by Istituto 'Mario Negri'. If a recruitment centre has none left, it must request a supply.
The Randomization Forms, Treatment Forms and Adverse Drug Reaction Forms are simple paper forms.
The **Baseline Form** and the **Follow-up Form,** on the other hand, are **self-copying forms**. They are grouped in sets containing on Baseline Form and two Follow-up

Forms. To make entries on them use only blue or black ball-point pens, NOT fountain-pens or pencils.

Answer the questions, from time to time, by marking the appropriate reply with an 'X' or writing in the space provided, in block capitals.

For all questions with YES or NO replies, one of the two possible replies must always be marked with an 'X'.

To correct an incorrect entry, cross it out and make the correct entry next to it, initialling and dating the correction. **DO NOT use correcting fluid.**

MONITOR

Each recruitment centre will be visited **at least three times** during the course of the study by a monitor (research assistant) who will have the role of supporting conducting of the study and the task of checking that the forms are properly completed.

The Investigator will be contacted to arrange an appointment, and **all the necessary time must be devoted to it**.

The monitor must be able to meet all the recruiting psychiatrists of the site during a single visit. To make this simpler, it is advisable to arrange the visits at time when it is easier to trace all the psychiatrists concerned will be present, e.g. on days on which regular meetings of the service are to be held.

FILING AND DESPATCH OF THE FORMS

The Recruitment Forms of the subjects included in the studied must be filed in their respective folders until the end of the study.

The Recruitment Forms of the excluded subjects must be filed by each treating psychiatrist in the special green folder (Excluded Patients Register). At the end of the year of recruitment, they shall be collected by the Principal Investigator, who will create the **Excluded Patients Register of the participating site**.

The Randomization Forms, Treatment Forms and ADR Report Form must be faxed to Istituto 'Mario Negri' (+39 02 39014300). The originals of the forms and sheets must, on the other hand, be kept at the recruitment centre in their respective folders. At the end of the trial stage and after being reviewed by the monitor, they will be collected by Istituto 'Mario Negri'.

Special care must be taken with regard to the **Treatment Forms** reporting **discontinuation of the treatment and the reasons for stopping,** which must faxed immediately to Istituto 'Mario Negri'.

As far as concerns the sets of **Baseline and Follow-up Forms**, the coloured copies (originals) of each self-copying set must be sent to Istituto 'Mario Negri' immediately after completion in a pre-stamped envelope, while the white copies must be kept by the participating site in the GiSAS Folder until the end of the study. The same procedure must be adopted for the **sheets for rating the BPRS and LUNSERS tests**.

The clinical documentation (results of blood chemistry tests, electrocardiograms and ECG reports) **must be photocopied and made anonymous**. They must then be kept in the GiSAS Folder, taking care to **mark each form with the patient code**.

One copy of all the documentation should be kept in the GiSAS Folder until the end of the study.

The procedures to be used by the GiSAS investigators for sending the forms and sheets to Istituto 'Mario Negri' are summarised in Table 2.

After the final visit by the monitor, all the documentation will be collected by Istituto 'Mario Negri'.

RECRUITMENT FORM

A Recruitment Form must be initiated for each patient entering the **screening stage.**

The Recruitment Form of each patient to be included in the trial must be completed, initialled and marked with the patient code (obtained by means of the telephone randomization procedure) and kept in the GiSAS Folder.

The Recruitment Forms of those who cannot be included, with no patient codes, must be kept in a special green folder (the Excluded Patients Register).

RANDOMIZATION FORM

A Randomization Form has to be completed for each patient included.

The Randomization Form **is not self-copying**. **The first side** contains the patient's main details and the randomization code, and must be **faxed to Istituto 'Mario Negri'** (+39 02 39014300) after the patient has taken the first dose of the drug assigned to him/her. **The second side**, containing confidential data, **must not be sent to Istituto 'Mario Negri'.**

Table 2. Procedures for sending in the forms

Fax	**Randomization Form** **Treatment Forms** **ADR Report Form**	*After the first dose of the drug* *Approximately once a month circa and whenever the treatment is altered* *At the onset of any adverse drug reaction*
Mail	**Baseline Form** (*original*) **Follow-up Form** (*original*) Coding form (*original*)	*After the baseline assessments* (t_0) *After the follow-up assessments* (t_1 t_2) *After the baseline and follow-up assessments* (t_0 t_1 t_2)

BASELINE FORM

The Baseline Form and two copies of the Follow-up Form make up a single **set of self-copying sheets** (set of Baseline and Follow-up Forms).

A Baseline Form must be completed by the treating psychiatrist for each patient who is randomised.

The **randomization number** (patient code) and the **date of completion of the form** must be shown clearly on it.

It contains information concerning (a) the patient's lifestyle, (b) his/her case history, (c) the drugs he/she was taking at the time of inclusion and (c) other clinically significant information.

The following must be copied onto it:

- the requested laboratory values (haemochrome, leukocyte formula and electrolytes);
- the patient's anthropometric and ECG data;
- the patient's GAF, BPRS and LUNSERS scores.

Lab and instrumental tests: The date on which the tests were carried out will have to be indicated, together with the values of all the parameters required, using the units of measurement indicated.

The date on which the tests were carried out:

(a) shall be prior to that of taking the first dose of the drug;

(b) shall NOT be more than 21 days earlier than the date of randomization.

The blood samples for the centralised laboratory must be identified by sticking **one of the labels provided** to the form.

First of all, the date of sampling must be entered. Then the two loose labels contained in each sampling kit and identical to those already attached to the test tubes must be put into place. One of the labels must be stuck to the coloured sheet (original to be sent to Istituto 'Mario Negri') and the other to the white sheet (copy to be kept at the site).

The date of sampling:

(a) shall be prior to that of taking the first dose of the drug;

(b) shall NOT be more than 21 days earlier than the date of randomization.

TREATMENT FORM

A Treatment Form **must be completed**:

(a) whenever a change is made in the antipsychotic treatment assigned and

(b) at least once a month.

The randomization number (patient code) and the date of completion must be shown clearly on the form.

All the Treatment Forms must be **faxed to Istituto 'Mario Negri'** (+39 02 39014300), taking care to send both the first and the second side.

To complete the Treatment Form correctly, it is necessary to refer to the **Monitoring Chart** (**Attachment 3**). This flow chart illustrates the decision-making process to be followed by the treating psychiatrist in order either to confirm the treatment assigned to the patient or to state that it has been stopped.

The Treatment Form is divided up into **four sections** (points 1, 2, 3 and 4): Section One investigates any changes in the antipsychotic treatment assigned, Section Two documents confirmation by the treating physician of the antipsychotic treatment assigned, Section Three investigates the presence of other drug treatment and Section Four records the reasons, if any, for discontinuing the antipsychotic treatment assigned (**Discontinuation Form**).

If the antipsychotic treatment assigned is found to be unchanged, it will be sufficient to answer the preliminary question by marking the YES box with a cross. It will not be necessary to complete the second section (point 1), and it will be possible to go directly to the next ones (points 2 and 3).

The **Discontinuation Form** (point 4) must be completed only **if the antipsychotic treatment assigned is stopped once and for all**. The **date and the reason for stopping treatment** must be indicated and a **follow-up examination** must be scheduled as soon as possible. A **deadline of 21 days** has been set within which to carry out the follow-up assessment, instrumental tests and the blood sampling.

FOLLOW-UP FORM

The Baseline Form and two copies of the Follow-up form make a single **set of self-copying sheets** (set of baseline and follow-up assessment forms).

A Follow-up Form must be completed by the treating psychiatrist for each patient randomised.

The **randomization number** (patient code) and the **date of completion of the form** must be shown clearly on it.

It contains information concerning (a) the patient's lifestyle, (b) the taking over of psychiatric care of the patient, and (c) the activities carried out in order to promote compliance with the prescribed treatment. **Reference must be made solely to the period following recruitment.**

Careful viewing of the information required at the time of the follow-up is recommended.

This is because although such information is acquired retrospectively, it will be necessary **to keep track of the data required throughout the duration of the study**, so as to avoid a reconstruction that might be too imprecise.

The following must be copied onto the form:

- the requested laboratory values (haemochrome, leukocyte formula and electrolytes);
- the patient's anthropometric and ECG data;
- the patient's GAF, BPRS and LUNSERS scores.

Lastly, taking of the blood samples for the centralised laboratory must be documented by sticking the special label to the form.

Lab and instrumental tests: The date on which the tests were carried out will have to be indicated, together with the values of all the parameters required, using the units of measurement indicated.

Taking of the **blood samples for the centralised laboratory** must be documented by sticking the special label to the form.

First of all, the date of sampling must be entered. Then the two loose labels contained in each sampling kit and identical to those already attached to the test tubes must be put into place. One of the labels must be stuck to the coloured sheet (original to be sent to Istituto 'Mario Negri') and the other to the white sheet (copy to be kept at the site).

Follow-up examination and the required tests must be scheduled on **two occasions**:

(a) at the time, if any, of **discontinuing the assigned antipsychotic treatment** (**follow-up I, t_1**);

(b) in **month 12 following randomization** (**follow-up II, t_2**).

In the first case, the examination, the tests and taking of the samples for the centralised laboratory must be scheduled at a distance of **21 days at the most after discontinuing the treatment**. In the second case, on the other hand, the follow-up may be scheduled at any time **between 7 days prior to the date set for the examination to 21 days after it.**

ADR REPORT FORM

Any detrimental or undesired reaction to medication during a trial, regardless of the dose administered is defined an **adverse drug reaction (ADR)**.

Any adverse reaction that, regardless of the dose, has a fatal outcome, endangers the life of the subject, entails hospitalisation or lengthens an existing stay in hospital, or which leads to an disability or a serious or long-term incompetence or to a congenital anomaly or malformation or a defect at birth is defined a **SERIOUS ADR**.

Spontaneous reporting of an ADR consists of notification concerning the onset of a symptom or of an upset suspected of having occurred after taking a drug.

All such occurrences must be reported by completing an ADR Report Form and faxing it to Istituto 'Mario Negri' (+39 02 39014300).

In accordance with Law Decree no. 211 of 24th June 2003, Istituto 'Mario Negri' has to take care of recording in detail all adverse events notified by the investigators and of reporting same to the Ethics Committee concerned and to the Ministry of Health.

In the event that the death of a subject is notified, the Investigator must inform both Istituto 'Mario Negri' and, directly, the Ethics Committee concerned, completing and sending them the ADR Report Form of the study and providing any additional information required.

In the event of serious Adverse Drug Reactions (ADR's):

An ADR Report Form must be faxed (to 39 02 39014300) **within 24 hours** from becoming aware of the event.

The up-dated form must be faxed **within 4 days** from gaining knowledge of the event, attaching the necessary documentation for validating the event (e.g. letter of discharge, instrumental or laboratory tests).

If the event lasts for over 4 days, please fax the up-dated form, attaching any additional documentation, **within 4 days from solution of the event**.

The originals of the form and of the documentation must be sent to Istituto 'Mario Negri' using a pre-stamped envelope.

In the event of several ADR's affecting the same patient, a separate form must be completed for each of these.

In the event of a serious ADR, one form must be completed for each event occurring **until 30 days after discontinuing the assigned treatment**.

PUBLICATION OF THE RESULTS

The data relating to the study are the **sole property of Istituto di Ricerche Farmacologiche 'Mario Negri'**. Access to the data in their entirely by the participating sites will be guaranteed.

Following approval by the Scientific Committee, Istituto 'Mario Negri' undertakes to publish a final report on the main results of the study.

The overall results will be made available to the single Investigators, who may use them in the name of the group of GiSAS investigators for teaching purposes, for presentations at congresses and scientific publications, subject to the prior consent of the Scientific Committee.

Istituto 'Mario Negri' and the Scientific Committee will schedule publication of a series of scientific papers on the main aspects of the trial. The investigators at the participating sites will be included among the authors of the main scientific paper in the form of a collective signature. Following publication of the results, the scientific data in their entirety will be made available to the scientific community.

GiSAS Investigators are encouraged to promote ancillary studies having the following characteristics: (a) they must be conducted on patients included in the GiSAS study; (b) they must involve or concern staff members involved in the GiSAS study; (C) they must not entail an excessive burden for the staff.

APPENDIX 2

Site code |__|__|__|

RECRUITMENT FORM (RF)

(*Please answer the following questions by marking the appropriate reply with a cross*)

PLACE OF RECRUITMENT:

⓪ Mental Healthcare Centre/out-patient
① Day Hospital
② Residential facility
③ Hospital ward/in-patient
④ Day Centre
⑤ At home

AGE	SEX	CLINICAL DIAGNOSIS
|__|__|	⓪ M ① F	_____

YEARS AT SCHOOL: |__|__|

MARITAL STATUS:

⓪ Never married
① Married
② Separated/divorced
③ Widow/widower

EMPLOYMENT STATUS:

⓪ Employed
① Protected employment
② Retired
③ Housewife/husband
④ Student
⑤ Unemployed
⑥ Disabled

MINI DIAGNOSIS (NOTE: The diagnosis is made by the clinician using the checklist of psychotic disorders of the *Mini International Neuropsychiatric Interview*, based on the criteria of DSM-IV)

Axis I _____

Axis II _____

Axis III _____

RECRUITMENT CHECKLIST

(*Please answer the following questions by marking the appropriate reply with a cross*)

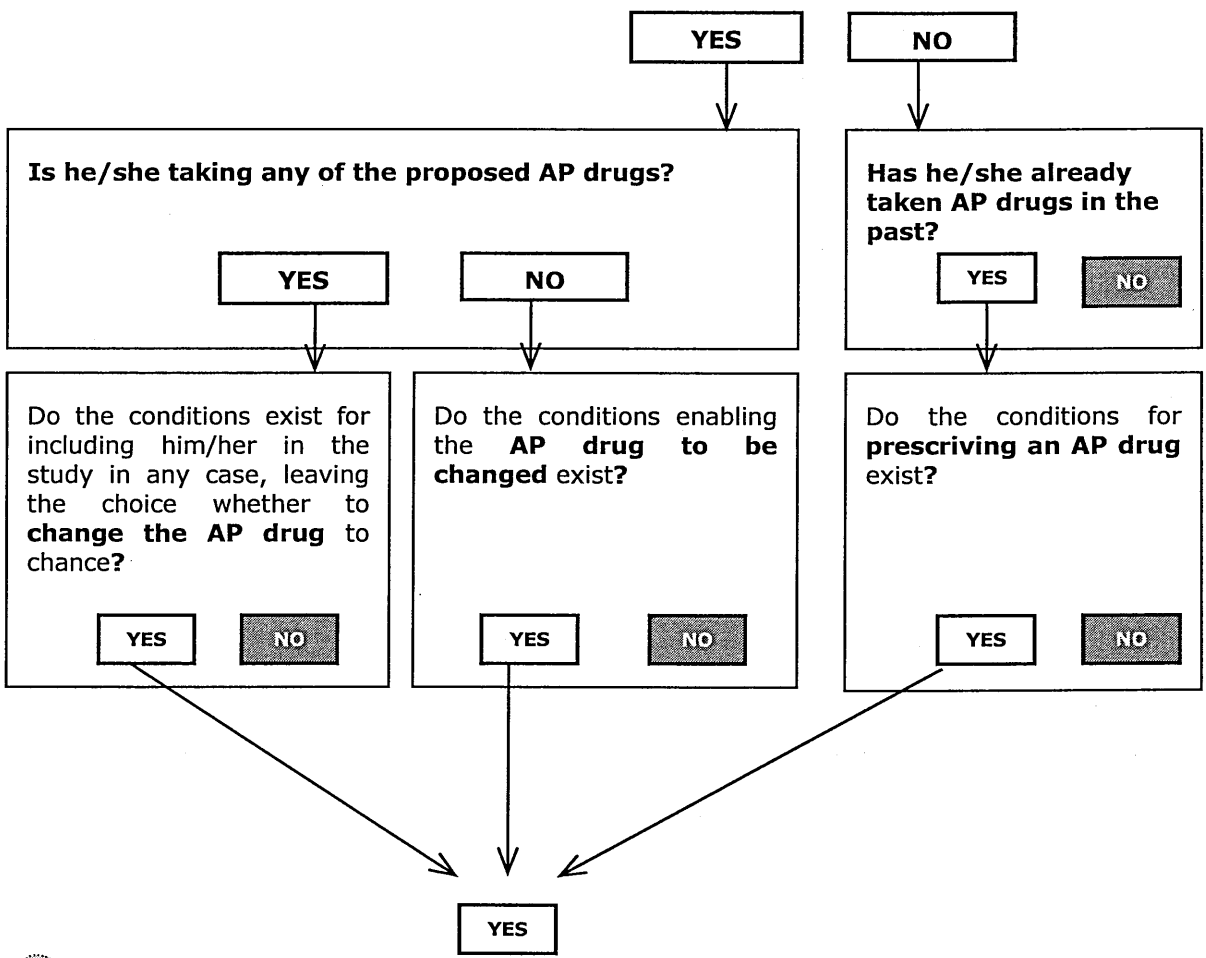
a) IS THE PATIENT **OF AGE?**

YES NO

b) DOES THE PATIENT HAVE **SCHIZOPHRENIA?**

YES NO

c) IS THE PATIENT TAKING **AP TREATMENT?**



! THE PATIENT IS TAKEN INTO CONSIDERATION FOR **INCLUSION IN THE STUDY**

I. DOES THE PATIENT HAVE **METABOLIC SYNDROME**? YES NO

II. DOES THE PATIENT HAVE **TYPE 2 DIABETES**? YES NO

III. ARE THERE **PARTICULAR PHYSICAL CONDITIONS OF THE PATIENT** CONTRAINDICATING HIS/HER INCLUSION IN THE STUDY? YES NO

IV. ARE THERE ANY CLEAR **CONTRAINDICATIONS TO THE USE OF ARIPIPRAZOLE**? YES NO

V. ARE THERE ANY CLEAR **CONTRAINDICATIONS TO THE USE OF OLANZAPINE**? YES NO

VI. ARE THERE ANY CLEAR **CONTRAINDICATIONS TO THE USE OF HALOPERIDOL**? YES NO

(*If there are any contraindications to use of any of the proposed drugs, specify them* _____ _____)

VII. IS IT NOT THOUGHT POSSIBLE TO **FOLLOW** THE PATIENT **FOR THE NEXT 12 MONTHS**? YES NO

IF EVEN ONLY ONE OF THE QUESTIONS HAS BEEN ANSWERED WITH A YES THE PATIENT **CANNOT BE INCLUDED IN THE STUDY**

DOES THE PATIENT AGREE TO TAKE PART IN THE STUDY? YES NO

IF SO, THE PATIENT IS INCLUDED IN THE STUDY
Proceed to complete the Randomisation Form

Completed on |__|__|__|__|__|__| (dd mm yy) **Patient code** |__|__|

TREATING PSYCHIATRIST **SIGNATURE**

_____ _____

APPENDIX 3

Site code |___|___|___| **Patient code** |___|___|

BASELINE FORM (BF)

(*Please answer the following questions by marking the appropriate reply with a*

Where does the patient live?

⓪ At home
① In a residential facility
② Other, specify: _____

With whom does the patient live?

⓪ On his/her own
① With family members
② With other people. Specify: _____

LIFESTYLES

(**N.B.** *Refer to the last year*)

DOES THE PATIENT:

DRINK ALCOHOL YES NO **SMOKE** YES NO **DRINK COFFEE** YES NO

If **SO**, *indicate his/her average daily consumption*:

wine (125-ml glasses) **n°** |__|__| Cigarettes **n°** |__|__| coffee-cups n° |__|__|
beer (33-cl cans) **n°** |__|__|
hard drinks (small glass) **n°** |__|__|

PHYSICAL ACTIVITY

AT WORK

0 **Sedentary** (e.g. clerical worker, student)
1 **Standing** (e.g. shop assistant, housewife, teacher)
2 **Average** (e.g. maid / manservant, cleaning)
3 **Heavy** (e.g.. gardener, farmer, industrial worker)
4 **Very heavy** (e.g. builder, demolition worker, sports)
5 ***Not workin***

IN FREE TIME

0 **Little exercise, sedentary** (e.g. reading, watching TV)
1 **Mild exercise** (e.g. short walks, yoga, riding a bicycle)
2 **Moderate exercise** (e.g. regular sports or open-air activity)
3 **Intense activity** (e.g. intense sports)

Site code |__|__|__| **Patient code** |__|__|

SIGNIFICANT CLINICAL ASPECTS

Year of first psychiatric contact |__|__|__|__| ☐ *Unknown*

Taken on by this service in the year |__|__|__|__| ☐ *Unknown*

Is the patient currently hospitalised in a psychiatric ward? **YES** **NO**

Is the patient currently addicted to substances or alcohol, or does he/she exhibit abuse thereof? **YES** **NO**

Has the patient ever attempted suicide in his/her lifetime? **YES** **NO**

If so, how many times? |__|__|

Year of last episode |__|__|__|__| ☐ *Unknown*

Does the patient have tardive dyskinesia? **YES** **NO**

Does the patient have other complaints traceable to drugs taken?

YES **NO**

If so, what complaints?

Drug	**Type of complaint** (diagnosis, if any)	**Drug**	**Type of complaint** (diagnosis, if any)

CASE HISTORY

MAJOR DISEASES: **CARDIOVASCULAR** YES NO

NEUROLOGICAL YES NO

OTHERS YES NO

If so, specify the diagnosis: _____

_____

Site code |___|___|___| **Patient code** |___|___|

PHARMACOLOGICAL TREATMENT

How long is it since the patient took an AP drug for the first time? |___|___| |___|___|
years *months*

PREVIOUS ANTIPSYCHOTIC TREATMENT (*refer to the last two years*)

Patient's compliance: ⓪ **unsatisfactory** ① **uncertain** ② **satisfactory** ③ ***not assessable***

Patient's overall opinion of earlier AP treatment

a) efficacy: ⓪ **very negative** ① **fairly negative** ② **fairly positive** ③ **very positive** ④ ***not assessable***

b) side effects: ⓪ **Very negative** ① **fairly negative** ② **fairly positive** ③ **very positive** ④ ***not assessable***

CURRENT PHARMACOLOGICAL TREATMENT (*refer to time of inclusion in the study*)

Is the patient receiving **oral antipsychotic treatment**? **YES** **NO**

If so, what drugs is he/she receiving?

Molecule	**Dose**	**Date of starting treatment**
1. _____	|___|___| mg/day	|___|___| mm yy
2. _____	|___|___| mg/day	|___|___| mm yy

Is the patient receiving **depot antipsychotic treatment**? **YES** **NO**

If so, what drugs is he/she receiving?

Molecule	**Dose**	**Interval**	**Date of last injection**
_____	|___|___| mg	every |___|___| weeks	|___|___|___| dd mm yy

Is the patient receiving any **other pharmacological treatment***? **YES** **NO**
(*consider any and all classes and categories of drugs, not only psychoactive drugs*)

If so, what drugs is he/she receiving?

Molecule	**Date of starting treatment**	**Molecule**	**Date of starting treatment**
1. _____	|___|___|___|___|	3. _____	|___|___|___|___|
2. _____	|___|___|___|___|	4. _____	|___|___|___|___|

* *The use of **LITHIUM** or other mood stabilisers is permitted only if it was started **at least 3 months prior to recruitment.***

Site code |___|___|___| **Patient code** |___|___|

CLINICAL EXAMINATION

Height |___|___|___| cm **Body weight** |___|___|___| kg

Abdominal circumference |___|___|___|,|___| cm

Hip circumference |___|___|___|,|___| cm

BP |___|___|___| / |___|___|___| mmHg

Report the presence of any of the **following disorders**:

Akathisia	YES	NO	Gynaecomastia	YES	NO
Parkinsonian state	YES	NO	Galactorrhea	YES	NO
Dystonia	YES	NO	Dysmenorrhea	YES	NO
Tardive dsykinesia	YES	NO	Irregular menstruation	YES	NO

ECG FINDING* **Date** |__|__|__|__|__|__| dd mm yy

HR |___|___|___| bpm **QT_C** |___|___|___| msec

Assessment of ECG: 0 **ABNORMAL** 1 **NORMAL**

If **ABNORMAL**, specify:

Atrial fibrillation/flutter	YES	NO	Right BBB	YES	NO
PM-induced rate	YES	NO	Left BBB	YES	NO
Pathological Q waves	YES	NO	LEFT ventricular hypertrophy	YES	NO

☐ Other. Specify: _____

BPRS 4.0 score** |___|___|___| **GAF** score** |___|___|___|

LUNSERS score** |___|___|___|

If NOT completed, state the reason: _____

* Keep **copies of the electrocardiogram and of the finding** in the GiSAS folder.

** Indicate the overall score of the scales and keep copies of them in the GiSAS folder.

Site code |___|___|___| **Patient code** |___|___|

BLOOD SAMPLES FOR THE CENTRALISED LABORATORY

(glucose, triglycerides, HDL cholesterol, prolactin)

Taken on |___|___|___|___|___|___|
dd mm yy

Stick the adhesive label from the sampling kit here

BLOOD TESTS

HAEMOCHROME WITH FORMULA* Sampling date |___|___|___|___|___|___|
dd mm yy

Haemochromocytometric tests

While blood cells (/mm^3) |___|___|___|___|___|

Red blood cells (/mm^3) |___| , |___| million

Platelets (/mm^3) |___|___|___|___|___|

Haemoglobin (g/dl) |___|___| , |___|

Haematocrit (%) |___|___|

Leukocyte formula

Neutrophils (%) |___|___|___|

Lymphocytes (%) |___|___|___|

Electrolytes

Na^+ (mEq/l) |___|___|___|

K^+ (mEq/l) |___|___|___|

Mg^{++} (mg/dl) |___|___|___|

Completed **on** |___|___|___|___|___|___|
dd mm yy

By _____ **Signature** _____

* Keep a **copy of the report** in the GiSAS folder.

APPENDIX 4

Site code |__|__|__| **Patient code** |__|__|__|

TREATMENT FORM (TF)

(Please answer the following questions by marking the appropriate reply with a cross)

WAS THE ASSIGNED DRUG TAKEN REGULARLY WITHOUT ADDING OF ANY OTHER ANTIPSYCHOTICS?

N.B. If so, skip the next Section and go to **POINT 2.**

YES NO

IS THE PATIENT CURRENTLY TAKING THE ASSIGNED ANTIPSYCHOTIC (AP) DRUG?
(See TREATMENT DIAGRAM)

☐ **YES,** he/she is taking it

HAVE THERE BEEN PERIODS SINCE THE LAST CHECK-UP IN WHICH HE/ SHE DID NOT TAKE THE AP?

☐ NO ☐ YES

If so, was it a *temporary and occasional* suspension *?

☐ YES ☐ NO → **DISCONTINUED**

☐ **NO,** he/she is not taking it

WAS IT A *TEMPORARY AND OCCASIONAL* DISCONTINUATION? *

☐ YES ☐ NO

DISCONTINUED

IS THE PATIENT CURRENTLY TAKING ANY OTHER AP's?** ☐ NO ☐ YES → **DISCONTINUED**

If so, which?_____ / ___|___ mg/day Start of treatment: |__|__|__|__|__|__| dd mm yy

_____ / ___|___ mg/day Start of treatment: |__|__|__|__|__|__| dd mm yy

If the patient **IS NOT TAKING ANY AP DRUG,** state why:

☐ Clinical remission ☐ *Temporary and occasional* discontinuation*

☐ Non-compliance ☐ All AP's contraindicated (*specify*:_____)

DURING TODAY'S CHECK-UP, WAS THE AP DRUG CONFIRMED AS MONOTHERAPY *?**

YES

The patient will **CONTINUE** to take the assigned AP drug

CURRENT DOSE: |___|___| **mg/day**

NO

The patient will **STOP** taking the assigned AP drug

FIX A **FOLLOW-UP** APPOINTMENT AS SOON AS POSSIBLE, COMPLETE THE **DRUG DISCONTINUATION FORM** AND **FAX** THIS FORM TO ISTITUTO 'MARIO NEGRI' (**Fax: +39 02 39014300**)

** Discontinuation is "temporary" if it lasts less than 2 weeks and "occasional" when it occurs only once in 6 months.*
*** Do not consider overlaps during titration (4 weeks from randomisation) or occasional parenteral therapy in case of need.*
**** The AP drug can be confirmed only if the treatment **DISCONTINUATION** criteria have **NOT** been met.*

HAVE ANY OTHER DRUGS BEEN STOPPED OR ADDED SINCE THE LAST FOLLOW-UP?
(*Consider every class and category of drugs - not just psychoactive drugs*)

YES ↓ NO

MOLECULE*		**DATE** (dd/mm/yy)
_____	☐ **START of treatment**	|__|__|__|__|__|__|
	☐ **END of treatment**	|__|__|__|__|__|__|
_____	☐ **START of treatment**	|__|__|__|__|__|__|
	☐ **END of treatment**	|__|__|__|__|__|__|
_____	☐ **START of treatment**	|__|__|__|__|__|__|
	☐ **END of treatment**	|__|__|__|__|__|__|
_____	☐ **START of treatment**	|__|__|__|__|__|__|
	☐ **END of treatment**	|__|__|__|__|__|__|
_____	☐ **START of treatment**	|__|__|__|__|__|__|
	☐ **END of treatment**	|__|__|__|__|__|__|

* *The use of **LITHIUM** or other mood stabilisers is permitted only if it was started **at least 3 months prior to recruitment.***

DRUG DISCONTINUATION MODULE

PLEASE MARK THE MAIN REASON FOR DRUG DISCONTINUATION

DISCONTINUATION Date: |__|__|__|__|__|__| (dd mm yy)

[0] LACK OF EFFICACY → ⓪ clinician's decision ① patient's decision ② shared decision

Please specify: _____

[1] POOR TOLERABILITY → ⓪ clinician's decision ① patient's decision ② shared decision

Please specify: _____

[2] PATIENT'S OWN INITIATIVE

Please specify: _____

[3] CLINICAL REMISSION → ⓪ clinician's decision ① patient's decision ② shared decision

Please specify: _____

Completed on |__|__|__|__|__|__| (dd mm yy)

By _____ **Signature** _____

APPENDIX 5

Site code |__|__|__| **Patient code** |__|__|

FOLLOW-UP FORM (FF)

(Please answer the following questions by marking the appropriate reply with a cross)

FOLLOW-UP DEADLINE

☐ DISCONTINUATION OF AP DRUG

DATE: |__|__|__|__|__|__| dd mm yy

☐ MONTH 12

WAS THE FOLLOW-UP EXAMINATION POSSIBLE*? NO YES

If NOT, state the reason:

[0] The patient has died
[1] The patient has withdrawn his/her consent
[2] The patient cannot be traced
[3] The time limits have expired*

* The examination and sampling must take place **not more than 21 days** after discontinuing the assigned AP treatment or following the end of the 12-month treatment period.

*If the patient is still taking the assigned AP drug **ONE YEAR LATER**, he/she will be asked the following question:*

Has the drug you have been taking for the last year (state the name)

(a) helped to make you feel better?

[0] NO, my ailments have worsened
[1] NO, the effect was insufficient
[2] I did not feel any effect
[3] YES, there has been some improvement
[4] YES, there has been a considerable improvement

(b) caused you any problems?

[0] YES, I found it very difficult to tolerate
[1] YES, it caused me several problems
[2] NO, it simply caused me some discomfort, but which I found tolerable
[3] NO, it did not cause me any discomfort

PHARMACOLOGICAL TREATMENT

Is the patient taking **ANTIHYPERTENSIN TREATMENT**? YES NO

Is the patient taking **INSULIN** or **HYPOGLYCAEMIC TREATMENT**? YES NO

Site code |___|___|___| **Patient code** |___|___|

CLINICAL EXAMINATION

Height |___|___|___| cm **Body weight** |___|___|___| kg

Abdominal circumference |___|___|___|,|___| cm

Hip circumference |___|___|___|,|___| cm

BP |___|___|___| / |___|___|___| mmHg

Report the presence of any of the **following disorders**

Akathisia	YES	NO	Gynaecomastia	YES	NO
Parkinsonian state	YES	NO	Galactorrhea	YES	NO
Dystonia	YES	NO	Dysmenorrhea	YES	NO
Tardive dsykinesia	YES	NO	Irregular menstruation	YES	NO

ECG FINDING* **Date** |__|__|__|__|__|__| dd mm yy

HR |___|___|___| bpm **QT_c** |___|___|___| msec

Assessment of ECG: 0 **ABNORMAL** 1 **NORMAL**

If **ABNORMAL**, specify:

Atrial fibrillation/flutter	YES	NO	Right Bundle Branch Block	YES	NO
PM-induced rhythm	YES	NO	Left Bundle Branch Block	YES	NO
Pathological Q waves	YES	NO	LEFT ventricular hypertrophy	YES	NO

☐ Other. Specify: _____

GAF score** |___|___|___| **LUNSERS score**** |___|___|___|

BLOOD SAMPLES FOR THE CENTRALISED LABORATORY

(glucose, triglycerides, HDL cholesterol, prolactin)

Taken on |__|__|__|__|__|__| dd mm yy

Stick the adhesive label from the sampling kit here

* Keep copies of the electrocardiogram and of the finding in the GiSAS folder

** Indicate the overall score of the scales and keep copies of them in the GiSAS folder

Site code |__|__|__| **Patient code** |__|__|

BLOOD CHEMISTRY TESTS

HAEMOCHROME WITH FORMULA Sampling date |__|__|__|__|__|__| dd mm yy

Haemochromocytometric tests

While blood cells (/mm^3) |__|__|__|__|__|

Red blood cells (/mm^3) |__|,|__| million

Platelets (/mm^3) |__|__|__|__|__|

Haemoglobin (g/dl) |__|__|,|__|

Haematocrit (%) |__|__|

Leukocyte formula

Neutrophils (%) |__|__|__|

Lymphocytes (%) |__|__|__|

Electrolytes

Na^+ (mEq/l) |__|__|__|

K^+ (mEq/l) |__|__|__|

Mg^{++} (mg/dl) |__|__|__|

LIFESTYLES

(**N.B.** *Refer* ***ONLY to the period following recruitment***)

CONSUMPTION OF

ALCOHOL YES NO **CIGARETTES** YES NO **COFFEE** YES NO

If **YES**, *indicate the average daily consumption*:

wine (125-ml glasses) **n°** |__|__|

beer (33-cl cans) **n°** |__|__|

hard drinks (small glass) **n°** |__|__|

Cigarettes **n°** |__|__|

coffee-cups **n°** |__|__|

PHYSICAL ACTIVITY

AT WORK

- 0 **Sedentary** (e.g. derical worker, student)
- 1 **Standing** (e.g. shop assistant, housewife, teacher)
- 2 **Average** (e.g. maid / manservant, deaning)
- 3 **Heavy** (e.g. gardener, farmer, industrial worker)
- 4 **Very heavy** (e.g. builder, demolition worker, sports)
- 5 ***Not working***

IN FREE TIME

- 0 **Little, sedentary** (e.g. reading, watching TV)
- 1 **Mild exercise** (e.g. short walks, yoga, riding a bicycle)
- 2 **Moderate exercise** (e.g. regular sports or open-air activity)
- 3 **Intense activity** (e.g. intense sports)

Has the patent attended psycho-educational weight management or diet improvement courses or activities?

YES **NO**

Has the patient controlled or changed his/her diet, even only partly, for reasons of weight or health (e.g. low-sodium or low-calorie diet)?

⓪ **NO, never** ① **YES, several times** ② **YES, always**

Site code |__|__|__| **Patient code** |__|__|

Has the patient been hospitalised after recruitment in a non-psychiatric ward? **YES** **NO**

If SO: a) due to what disease: _____

b) Was the patient subsequently transferred to a non-psychiatric long-stay ward or residential facility? **YES** **NO**

TAKING THE PATIENT INTO PSYCHIATRIC CARE

(**N.B.** *Report events occurring **AFTER RECRUITMENT***)

Has the patient been hospitalised in a psychiatric ward, **day hospital or 24-hr Mental Health Unit or other service for acute patents**? **YES** **NO**

Has the patient been admitted to a **RESIDENTIAL FACILITY**? **YES** **NO**

Has the patient attended a **DAYCARE CENTRE**? **YES** **NO**

If the answer to any of the foregoing questions is in the affirmative, specify:

(0=Psychiatric ward; 1=Day hospital; 2= 24-hr Mental Health Unit; 3= Other service for acute patients; 4= Residential facility; 5= Day-care centre)

Site	Period (dd/mm/yy)	Site	Period (dd/mm/yy)
|__| |__|__|__|__|__|__| → |__|__|__|__|__|__|	|__| |__|__|__|__|__|__| → |__|__|__|__|__|__|
|__| |__|__|__|__|__|__| → |__|__|__|__|__|__|	|__| |__|__|__|__|__|__| → |__|__|__|__|__|__|
|__| |__|__|__|__|__|__| → |__|__|__|__|__|__|	|__| |__|__|__|__|__|__| → |__|__|__|__|__|__|
|__| |__|__|__|__|__|__| → |__|__|__|__|__|__|	|__| |__|__|__|__|__|__| → |__|__|__|__|__|__|

How many times has the patient been seen by the **TREATING PSYCHIATRIST**? **n°** |__|__|__|

Site code |___|___|___| **Patient code** |___|___|

Has the patient had contacts with **OTHER PROFILES?** YES NO
(**N.B.** *DO not consider any periods spent in hospital or in residential facilities*)

IF SO, which? (*always mark one of the two possible replies with a cross*)

1) Psychologist	YES NO	**IF SO,:** ⓪ occasionally ① regularly	specify:	⓪ private specialist ① health service
2) Another psychiatrist	YES NO	**IF SO,:** ⓪ occasionally ① regularly	specify:	⓪ private specialist ① health service
3) Nurse	YES NO	**IF SO,:** ⓪ occasionally ① regularly		
4) Educator/rehab personnel	YES NO	**IF SO,:** ⓪ occasionally ① regularly		
5) Other healthcare professional	YES NO	**IF SO,:** ⓪ occasionally ① regularly		
6) Other social care professional	YES NO	**IF SO,:** ⓪ occasionally ① regularly		
7) Social worker	YES NO	**IF SO,:** ⓪ occasionally ① regularly		
8) GP	YES NO	**IF SO,:** ⓪ occasionally ① regularly		

ACTIVITIES (*always mark one of the two possible replies with a cross*)

1. Psychiatric interviews YES NO

2. Psychological support interviews YES NO
   IF SO, specify: ⓪ occasionally ① regularly

3. Individual psychotherapy YES NO

4. Group psychotherapy YES NO

5. Interviews with family members YES NO
   IF SO, specify: ⓪ occasionally ① regularly

6. Specific family support activities YES NO

IF SO, specify:	YES	NO		YES	NO
Psycho-educational activities	o	o	Multi-family groups	o	o
Family therapy	o	o	Other	o	o

7. Job introduction/support YES NO

IF SO, specify:	YES	NO		YES	NO
Preparatory courses or training	o	o	Job introduction	o	o
Job support	o	o	Other	o	o

8. Other rehab activities YES NO

IF SO, specify:	YES	NO		YES	NO
Expressive activity groups	o	o	Discussion groups	o	o
Social skills	o	o	Daily life skills	o	o
Structured recreational activities	o	o	Supported housing	o	o

9. Attendance of self-help groups YES NO

10. Home visits or activities YES NO
    IF SO, how many times? **n°** |___|___|___|

Site code |__|__|__| **Patient code** |__|__|

ACTIVITIES FOR PROMOTING PATIENT COMPLIANCE WITH THE ASSIGNED TREATMENT, AFTER RECRUITMENT

(always mark one of the two possible replies with a cross and refer only to SPECIFIC NOT OCCASIONAL ACTIVITIES):

1. STRATEGIES FOR IMPROVING THE THERAPEUTIC ALLIANCE

Has the patient's personal experience and his/her subjective perception of both the beneficial and undesired effects of the AP treatment been investigated?	YES	NO
Have the goals of the AP treatment been shared with the patient?	YES	NO
Has the patient been involved in planning and monitoring the AP therapy?	YES	NO

2. BEHAVIOURAL INTERVENTIONS

a) for improving attendance of follow-up examinations

Has the patient received regular telephone or mailed reminders?	YES	NO
Has the patient been permitted to come for visits even without an appointment?	YES	NO
Has the patient been provided with guidance brochures?	YES	NO
Have the procedures for accessing the service been negotiated with the patient? (e.g. appointments always at the same time and on the same day of the week)	YES	NO

b) for improving daily compliance with the prescribed treatment

Has the dosage been optimised and the manner of taking the doses simplified?	YES	NO
Has the treatment been delivered to the patient in a loose form or in a customised pack?	YES	NO
Has the treatment been administered directly to the patient by a staff member?	YES	NO
Has administration of the treatment been entrusted to a family member?	YES	NO

3. PSYCHO-EDUCATIONAL INTERVENTIONS

Has a psycho-educational activity been conducted with regard to compliance with AP treatment?	YES	NO

If so: ☐ individual ☐ group

4. PSYCHOTHERAPY

Has a psychotherapeutic activity been conducted to improve the patient's motivation and insight?	YES	NO

If so: ☐ cognitive ☐ short psychodynamic ☐ motivational therapy

5. SOCIAL AND FAMILY SUPPORT INTERVENTIONS

Have the patient's family been involved in planning and monitoring the AP treatment?	YES	NO
Have the goals of the pharmacological treatment been shared with the patient's family?	YES	NO
Has a family psycho-educational activity been conducted?	YES	NO
Have specific activities been conducted to improve the patient's social network?	YES	NO

6. ORGANISATIONAL STRATEGIES

When the patient was discharged from hospital or residential facility, was he/she placed in contact with the community mental health team?	YES	NO
Has an integrated treatment for both the schizophrenia and the substance abuse been implemented?	YES	NO

Completed **on** |__|__|__|__|__|__| dd mm yy

by _____ **Signature** _____

APPENDIX 6

SURVEY ON RANDOMIZED CLINICAL TRIALS (RCT) IN SCHIZOPHRENIA

The present survey is addressed to all the clinicians working in the centers where GiSAS trial has been activated, NOT ONLY TO THOSE WHO ARE CURRENTLY INVOLVED IN THE STUDY

Code |__|__|__| **Date** |__|__|__|__|__|__| **Age** |__|__|

Gender ☐ M ☐ F **Years of psychiatric clinical activity** |__|__|

1. Setting of your clinical activity:

- ☐ Inpatients acute ward
- ☐ Outpatient clinic
- ☐ Residential facility

2. Are official guidelines for the treatment of schizophrenia adopted in your Department?

- ☐ **YES**
- ☐ **NO**

3. Did you ever take part to a RCT on schizophrenia?
Do not consider participation in the GiSAS trial.

- ☐ **YES**
- ☐ **NO**

If YES, please specify the number of RCT you took part to:

INDEPENDENT STUDIES	INDUSTRY-SPONSORED STUDIES
n° |__|__|	n° |__|__|

If NOT, why? *Please check just 1 box*

- ☐ I don't have time
- ☐ No one ever ask me to participate
- ☐ I don't think that casual assignment of treatment (randomization) is appropriate
- ☐ I don't think participation could lead to an improvement of my clinical practice
- ☐ I've never received interesting proposals

4. Did you ever take part to RCTs on non-pharmacological interventions in schizophrenia?

- ☐ **YES**
- ☐ **NO**

5. In your opinion, which are the main problems with subjects recruitment in a pharmacological RCT on schizophrenia?
Please number 3 answers from 1 to 3 in order of decreased importance

- ..... Difficulties in obtaining patient's informed consent
- ..... Poor patient's cooperation
- ..... The fear of recurrence
- ..... Time constraints
- ..... The study protocol limits clinical choiches
- ..... Fear of losing therapeutic alliance
- ..... Ethical doubts about randomization
- ..... Fear of legal consequences
- ..... The colleagues are not well disposed towards participation
- ..... Inclusion/exclusion criteria
- ..... To change current medication

6. In your opinion, why are currently being implemented RCT on schizophrenia?
Please check just 1 box

- ☐ To objectively evaluate drugs' effectiveness and tolerability
- ☐ To let the drugs being prescribed regardless of the final results
- ☐ To develop scientific evidence with the aim to improve clinical practice
- ☐ to get results that promote the new drugs

7. Have you been adequately informed about GiSAS trial?
Please check just 1 box

- ☐ YES, I received much information
- ☐ YES, I received sufficient information
- ☐ NO, I did not receive sufficient information
- ☐ NO, I did not receive information at all

8. In your opinion, which is the main difficulty that faces the clinician taking part to the GiSAS trial?
Please check just 1 box

- ☐ I'm not aware of the study
- ☐ Problems with the prescription of an antipsychotic monotherapy
- ☐ The 3 study drugs are hardly considered smilar
- ☐ To have no choice in regard to the antipsychotic prescribed
- ☐ The complexity of study protocol and procedures
- ☐ The only inclusion of schizophrenic patients
- ☐ previous negative experiences with the study drugs
- ☐ It is hard to implement a RCT in the rountine of Italian mental health services

9. Are you currently involved in the recruitment for GiSAS trial?

- ☐ Yes
- ☐ NO

If Yes, did you succeed in including at least 1 subject?

- ☐ YES
- ☐ NO

10. Based on your knowledge and experience, please number the following 3 drugs both in order of better efficacy and of better tolerability.
Please indicate with number 1 the best medication and go ahead with 2 and 3. If you consider two or more of them to be equivalent assign them the same number.

EFFICACY		**TOLERABILITY**	
.....	HALOPERIDOL	.....	HALOPERIDOL
.....	OLANZAPINE	.....	OLANZAPINE
.....	ARIPIPRAZOLE	.....	ARIPIPRAZOLE

11. Based on your experience, which is the best antipsychotic drug?
Please consider all the drugs at your disposal

12. Not taking into account clozapine, do you think there are differences in terms of effectiveness between first- and second-generation antipsychotics?
Please check just 1 box

- ☐ YES, first-generation antipsychotics are more effective
- ☐ YES, second-generation antipsychotics are more effective
- ☐ NO, there are no differences in terms of effectiveness

13. Not taking into account clozapine, do you think there are differences in terms of tolerability between first- and second-generation antipsychotics?
Please check just 1 box

- ☐ YES, first-generation antipsychotics are more tolerable
- ☐ YES, second-generation antipsychotics are more tolerable
- ☐ NO, there are no differences in terms of tolerability

14. What does mainly influence you in the choice of the antipsychotic drug for a patient affected by schizophrenia?
Please number 3 answers from 1 to 3 in order of decreased importance

- ..... Evidence based efficacy
- ..... Patient's medication adherence
- ..... Drug tolerability
- ..... Patient's preference
- ..... Drug dosage and formulations
- ..... My personal evaluation of drug effects

15. Which is your main source of knowledge and information on the use of antipsychotic medication?
Please number 3 answers from 1 to 3 in order of decreased importance

- ..... Personal reading of scientific publications
- ..... Attending conferences
- ..... Information by drug-company representatives
- ..... Personal clinical experience and sharing information with colleagues
- ..... Label indications and AIFA warnings

APPENDIX 7

TREATMENT RETENTION WITH REBOXETINE IN YEARS 2000-2006: A PHARMACO-EPIDEMIOLOGICAL COMPARATIVE STUDY.

Reboxetine has been used since 1997 for the treatment of depression in many European countries. It is supposed to act by binding to the noradrenaline transporter and blocking the reuptake of extracellular noradrenaline. Although reboxetine has been claimed to show superior efficacy than placebo and similar efficacy to SSRIs, its clinical relevance was questioned, and its preliminary approval was declined by US Food and Drug Administration (FDA) in 2001 [1].

In a recent report on newer antidepressants of the German Institute for Quality and Efficiency in Health Care (IQWiG), while mirtazapine and bupropion proved to be effective in alleviating symptoms, reboxetine resulted ineffective and potentially harmful [2]. The main findings of the meta-analysis on reboxetine were recently published on the British Medical Journal [3]. This paper by Edyng and colleagues provides an emblematic example of publication bias, in which the previously favourable evidence on the risk-benefit profile of reboxetine was overturned by the addition of unpublished data. Thirteen short-term randomised clinical trials (RCTs) of reboxetine against placebo or selective serotonin reuptake inhibitors (SSRIs), comprising a total of 4098 patients, were analysed, of these, data on 3033 subjects were unpublished. In the reboxetine versus placebo comparison no significant differences in remission rates were shown, but reboxetine was inferior for harm outcomes. Moreover, reboxetine was inferior to SSRIs, and, in particular, it was inferior to paroxetine for response and remission rates and to fluoxetine for withdrawals owing to adverse events. The authors included an additional analysis showing that published evidence overestimated reboxetine efficacy while underestimating harm [3]. This typical effect of publication bias was highlighted in other recent research on antidepressants [4, 5]. Turner and

colleagues (2008) reported that among 74 FDA-registered RCTs on antidepressants 31%, accounting for 3449 study participants, were not published [4]. According to the published literature 94% of the trials on antidepressants were positive, but only 51% were positive when unpublished studies were included. Separate meta-analyses of the published and unpublished data sets showed that the increase in effect size ranged from 11 to 69% for individual drugs and that was 32% overall [4].

In most European countries, including Italy, antidepressant prescribing doubled from 1993 to 2002, and within this rise, the use of selective serotonin reuptake inhibitors (SSRIs) increased tenfold [6]. Had clinicians known for the past two decades that the evidence for effectiveness was inflated perhaps they would have been more judicious in their use of antidepressants [7]. The case of reboxetine, however, seems to represent an exception. As was already pointed out by Edyng and colleagues (2010), in fact, reboxetine has a very small market share in Europe [8, 9]. Thus, it would appear that over the last decade the prescribing clinicians have voted against its use. Market success can be influenced by a number of factors other than drug's efficacy. Nevertheless, we can hypothesize that reboxetine poor effectiveness may have played a role in its commercial failure. In particular, a lower prescription trend might be associated with a higher rate of drug discontinuation which in turn could be interpreted as an indicator of ineffectiveness. The case of reboxetine represented therefore a singular and unique occasion to test out if a lack of efficacy would have been reflected over the years by a higher proportion of premature drug discontinuations.

The present analysis aimed to compare the use of reboxetine with that of fluoxetine and paroxetine in a large population sample in northern Italy. Trends of antidepressants' utilization from 2000 to 2006 and rates of prolonged and persistent use were compared. A secondary aim was to compare reboxetine prescribing trends with those of mirtazapine, another newer antidepressant with a very similar history in

terms of approval for marketing and admission to reimbursement by the Italian National Health Service (SSN).

In Italy, only between 1999 and 2001 were most second-generation antidepressants (including SSRIs and reboxetine) admitted for full reimbursement by NHS without restrictions. Thus, only since year 2000 are regional drug administrative data free from bias related to reimbursement restrictions and can be reliably used to evaluate and compare antidepressants' utilization in primary and secondary healthcare [10].

An analysis of the prescriptions of reboxetine, fluoxetine, paroxetine and mirtazapine to the adult population (18-65 years) of three Italian administrative provinces was performed. The study catchment area includes both rural and urban contexts and comprises nearly 30% of the population of Lombardy. In particular, the present study employed a population-based dataset containing prescribing records for 1 704 923 inhabitants from January 1, 2000 to December 31, 2007. It is part of a pharmaco-epidemiological collaborative project on drug prescription in Lombardy (the EPIFARM-Elderly Project). The structure of this database, routinely updated for administrative reasons, has been described in details elsewhere [11]. Briefly, for a drugs to be reimbursed by the NHS patients need a prescription from their general practitioner (GP) or a specialist and then get the medicines free of charge from retail pharmacies. Each local pharmacy provides these prescriptions to the Regional Health Authority to get reimbursed. Finally, the Regional Health Authority electronically stores these prescriptions into the Regional Drug Administrative Database.

We defined antidepressant "use" as the proportion of those who had at least one recorded prescription. We then distinguished those who were prescribed at least four drug packages ("prolonged use") from the rest of the group ("occasional use").

Since the premature discontinuation of the prescribed antidepressant can be considered a direct consequence of treatment failure related to adverse events or lack of therapeutic effect, persistence was adopted as a proxy indicator of effectiveness. To

identify the annual rates of persistence, we selected those who had (a) at least one recorded prescription, (b) no prescriptions in the previous year and (c) a treatment duration of at least six months. Since information on the individual dosage regimen was missing, we considered adequate the consecutive prescription of at least 6 drug packages within 8 months from the first dispensing which for reboxetine corresponded to a trial of 180 consecutive defined daily doses [12].

To analyse changes over time of the proportion of prolonged to occasional use and of persistence to non-persistence a Cochran-Armitage test for trend was used, splitting the Chi-squared value to obtain a test for the presence of a linear trend and a test for the deviation from linearity [13]. We then calculated the mean yearly rate of change in the proportion of prolonged to occasional use [14].

Differences in terms of prolonged and persistent use between reboxetine, fluoxetine and paroxetine were calculated through Chi-square tests; odds ratios (ORs) and confidence intervals (CIs) were calculated. A Hochberg adjustment was used to take into account the presence of multiple comparisons.

Logistic regression analyses were used to study the evolution of the incidence of antidepressant using calendar year as a continuous variable. The different antidepressants were compared in terms of mean annual incidence and slope of annual incidence. ORs are reported taking paroxetine as the reference category. Tests were done using JMP version 9.0, SAS Institute Inc.

Across the study period, the mean number of subjects per year who were prescribed and dispensed at least one of the study drug was 211 883. Figure 1 shows the annual prevalence rates of the use and of the prolonged use of the four study drugs from 2000 to 2006. The use of paroxetine and fluoxetine peaked in 2002 and then slightly decreased. On the whole, however, the growth of the prescriptions of both SSRIs was dramatic: from 0.42% to 1.16% for paroxetine, and from 0.18% to 0.39% for

fluoxetine. The prescripition rates of mirtazapine gradually increased all through the study period: from 0.07% in 2000 to 0.13% in 2006. On the contrary, the prescription rates of reboxetine showed a different trend and progressively decreased from 0.20% in 2000 to 0.04% in 2006.

Table 1 shows the annual rates of prolonged and persistent use for reboxetine, fluoxetine and paroxetine from 2000 to 2006. The overall proportion of prolonged to occasional use was significantly lower for reboxetine (42%) than for paroxetine (57%; OR 0.55, 95% CI 0.53/0.57, Chi-square, $p<0.001$, Hochberg adjusted) and fluoxetine (58%; OR 0.53, 95% CI 0.51/0.55, Chi-square, $p<0.001$, Hochberg adjusted). The annual rates of the prolonged use of paroxetine and fluoxetine were very similar and showed comparable changes. For both drugs, rates significantly increased over time: from 58% in 2000 to 63% in 2006 (test for trend, $p<0.001$). These annual changes, however, were characterised by a highly significant heterogeneity (deviation from linearity, $p<0.001$). Also reboxetine prolonged use showed a statistically significant growth: from 33% in 2000 to 52% in 2006 (test for trend, $p<0.001$). It increased by 4% per year with no significant deviation from linearity (deviation from linearity, $p=0.98$). The overall proportion of persistence to non-persistence was significantly lower for reboxetine (23%) than for paroxetine (34%; OR 0.60, 95% CI 0.56/0.64, $p<0.001$, Hochberg adjusted) and fluoxetine (36%; OR 0.53, 95% CI 0.49/0.57, $p<0.001$, Hochberg adjusted). The annual rates of persistence ranged 21-27% for reboxetine, 28-43% for paroxetine and 30-46% for fluoxetine. There was a certain fluctuation in annual rates of non-persistence and no significant time trends were evident. As shown in Figure 2, incident use of reboxetine, fluoxetine and paroxetine significantly decreased from 2000 to 2006 ($p<0.001$ for each of the three drugs). Both reboxetine and fluoxetine had lower mean incidence rates than paroxetine (fluoxetine: OR 0.40, 95% IC 0.40-0.41; reboxetine: OR 0.07, 95% IC 0.07-0.07). Similarly, more pronounced decreasing trends were observed for reboxetine and fluoxetine if

compared with paroxetine (fluoxetine: OR 0.96, 95% IC 0.95-0.97; reboxetine: OR 0.81, 95% IC 0.080-0.83). In particular, reboxetine showed the most relevant decrease in incident use: from 0.97‰ in 2001 to 0.19‰ in 2006.

Our results showed, for reboxetine, a progressive fall of the prescriptions in years 2000-2006 and higher treatment discontinuation rates than for fluoxetine and paroxetine. Reboxetine was the only antidepressant showing a decrease of the absolute number of users. Compared with fluoxetine and paroxetine, moreover, reboxetine had the most significant annual decrease of new prescriptions and the lowest rates of prolonged and persistent use. Thus, the use of reboxetine showed a decline in terms of prevalence and incidence and was associated with higher discontinuation rates at both the initiation and the maintenance phase of treatment.

The major strength of the present study is the reliability of the prescription data. The study dataset, in fact, included all the reimbursable prescriptions which were issued by GPs and specialists and were subsequently collected by patients in local pharmacies. A first study limitation is the absence of clinical data that did not allow to detect those who received antidepressant prescription properly. Moreover, although our records reflect both drug prescription and dispensing, no information on whether the study subjects eventually took the prescribed drugs was available. Finally, data are observational and we were not able to control for confounder at the patient level.

		Year						
		2000	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**
Reboxetine								
prolonged use	(%)	33.14	41.25	46.10	49.84	49.85	51.24	52.19
persistent use	(%)	-	20.70	25.06	22.74	25.40	26.75	22.80
Fluoxetine								
prolonged use	(%)	57.74	59.12	56.11	57.12	56.34	59.06	62.85
persistent use	(%)	-	45.62	32.21	29.51	31.61	35.35	38.37
Paroxetine								
prolonged use	(%)	58.44	55.71	55.02	54.94	57.15	59.94	62.92
persistent use	(%)	-	42.92	29.94	27.97	28.89	32.29	33.33
Adult population*	(no.)	1 703 353	1 704 923	1 698 923	1 695 262	1 683 385	1 667 979	1 646 700
AD prevalent users**	(no.)	13 661	32 299	34 354	31 171	29 933	27 140	26 125
AD incident users***	(no.)	-	26 394	19 235	15 356	14 401	12 068	11 221

*All subjects aged 18-65 living in the study areas;
**Subjects with at least one prescription of one of the three antidepressants (AD) in the reference year;
***Subjects with at least one prescription of one of the three antidepressants (AD) in the reference year and without any recorded prescription in the previous year.

Table 1. Annual proportions of prolonged to occasional use and of persistence to non-persistence of reboxetine, paroxetine, and fluoxetine from 2000 to 2006 in the three administrative provinces.

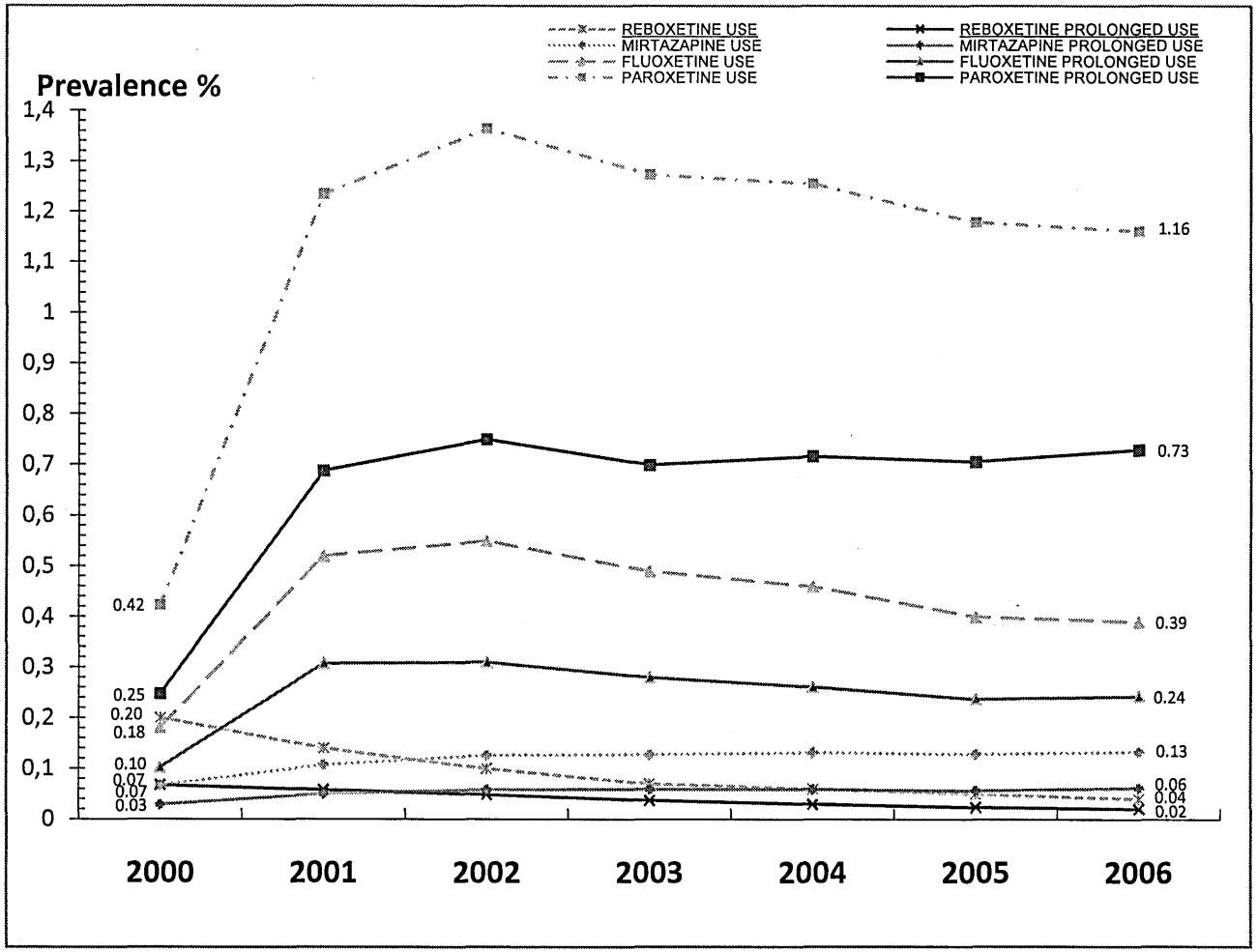


Fig 1. Prevalence rates per 100 inhabitants per year of the prescriptions of reboxetine, paroxetine, fluoxetine, and mirtazapine in the three administrative provinces.

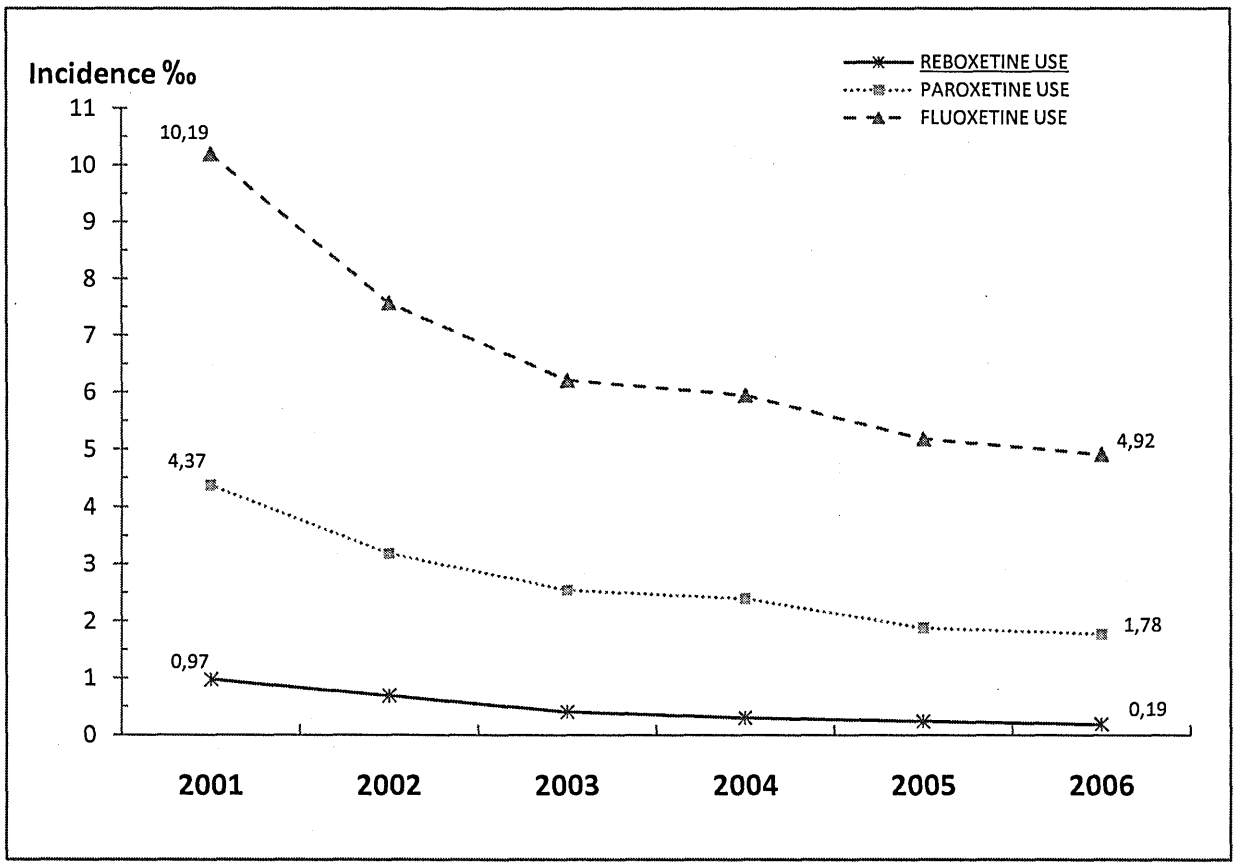


Fig 2. Incidence rates per 1000 inhabitants per year of the new prescriptions of reboxetine, paroxetine, and fluoxetine in the three administrative provinces.

Fluoxetine and paroxetine showed an increase in their prescriptions from 2000 to 2006. The increase of their prevalent use, however, was not mirrored by incident use, which significantly decreased. The discordance observed between prevalent and incident use is consistent with previous studies and has been explained by the persistence of antidepressant treatment [15, 16]. Namely, it is not that more people are being prescribed antidepressants but that treatment periods have became longer. Furthermore, the decrease in rates of new prescriptions can be interpreted as a consequence of the burst of growth observed for fluoxetine and paroxetine between 2000 and 2001.

In year 2000 the prescription rates of reboxetine and fluoxetine were very similar, but afterwards something changed. As was pointed out in previous work, the change of drug reimbursement policies could reliably explain the peak of SSRIs' prescriptions between 2001 and 2002 [10]. The same effect, however, was not evident for reboxetine. Moreover, while reboxetine is still an expensive brand-name antidepressant both paroxetine and fluoxetine went off patent during the study period and it is unlikely that the drug companies had incentive to promote them [17]. The comparison between reboxetine and mirtazapine gave unexpected results. The prescription rates of the two drugs had completely reversed trends, and again this can hardly be ascribed to marketing factors. What lies, then, behind the decline of reboxetine prescriptions?

Our findings, although being observational, are consistent with those of Eyding et al. (2010) [3]. In their meta-analysis, outpatient setting was highlighted as the strongest negative effect modifier for reboxetine. This could partly explain our results since virtually all subjects were community-dwelling adults and GPs accounted for more than 90% of antidepressant prescriptions. Moreover, we can hypothesize that the higher discontinuation rates of reboxetine have affected its perception as a poorly effective antidepressant and that this resulted in the decline of its prescriptions.

References

1. Preskorn SH. Reboxetine: a norepinephrine selective reuptake pump inhibitor. J Psychiatr Pract 2004, 10:57-63.

2. Institute for Quality and Efficiency in Health Care (IQWiG). [Bupropion, mirtazapine and reboxetine in the treatment of depression: final report; commission no A05-20C] [German]. 2009. https://www.iqwig.de/download/A05-20C_Abschlussbericht_Bupropion_Mirtazapin_und_Reboxetin_bei_Depressionen.pdf. Access verified 22/03/2011

3. Eyding D, Lelgemann M, Grouven U, Härter M, Kromp M, Kaiser T. Reboxetine for acute treatment of major depression: systematic review and meta-analysis of published and unpublished placebo and selective serotonin reuptake inhibitor controlled trials. BMJ 2010, 341:c4737.

4. Turner EH, Matthews AM, Linardatos E, Tell RA, Rosenthal R. Selective publication of antidepressant trials and its influence on apparent efficacy. N Engl J Med 2008, 358:252-60.

5. Whittington CJ, Kendall T, Fonagy P, Cottrell D, Cotgrove A, Boddington E. Selective serotonin reuptake inhibitors in childhood depression: systematic review of published versus unpublished data. Lancet 2004, 363:1341-1345.

6. Knapp M, McDaid D, Mossialos E, Thornicroft G. Mental health Policy and practice across Europe: an overview. In: Knapp M, McDaid D, Mossialos E, Thornicroft G, Editors, *The future direction of mental health care*, Open University Press, Milton Keynes, UK (2007), pp. 1-14.

7. Ghaemi SN. The failure to know what isn't known: negative publication bias with lamotrigine and a glimpse inside peer review. Evid Based Ment Health 2009, 12:65-68.

8. Schwabe U, Paffrath D. [Drug prescription report] [German]. Springer, 2009.

9. OsMed Working Group. [The use of drugs in Italy. National report year 2009] [Italian]. Il Pensiero Scientifico Editore, 2010. http://www.agenziafarmaco.it/it/content/rapporti-osmed-luso-dei-farmaci-italia. Access verified 22/03/2011.

10. Poluzzi E, Motola D, Silvani C, De Ponti F, Vaccheri A, Montanaro N. Prescriptions of antidepressants in primary care in Italy: pattern of use after admission of selective serotonin reuptake inhibitors for reimbursement. Eur J Clin Pharmacol 2004, 59:825-831.

11. Percudani M, Barbui C, Fortino I, Petrovich L. Antidepressant drug use in Lombardy, Italy: a population-based study. J Affect Disord 2004, 83:169–175.

12. Melfi CA, Chawla AJ, Croghan TW, Hanna MP, Kennedy S, Sredl K. The effects of adherence to antidepressant treatment guidelines on relapse and recurrence of depression. Arch Gen Psychiatry 1998, 55:1128-1132.

13. Armitage P. Tests for Linear Trends in Proportions and Frequencies. Biometrics 1955, 11:375-386.

14. Steel RGD, Torrie JH, Dickey DA. *Principles and Procedures of Statistics: A Biometrical Approach*. McGraw-Hill Inc, New York, (NY) 1996, pp. 520-1.

15. Moore M, Yuen HM, Dunn N, Mullee MA, Maskell J, Kendrick T. Explaining the rise in antidepressant prescribing: a descriptive study using the general practice research database. BMJ. BMJ 2009, 339:b3999.

16. Raymond CB, Morgan SG, Caetano PA. Antidepressant utilization in British Columbia from 1996 to 2004: increasing prevalence but not incidence. Psychiatr Serv 2007, 58:79-84.

17. Hansen RA, Chen SY, Gaynes BN, Maciejewski ML. Relationship of pharmaceutical promotion to antidepressant switching and adherence: a retrospective cohort study. Psychiatr Serv 2010, 61:1232-1238.